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NEWCASTLE-UPON-TYNE
COLLEGE OF MEDICINE

TWENTIETH CENTURY PRACTICE

AN INTERNATIONAL ENCYCLOPEDIA

OF

MODERN MEDICAL SCIENCE

BY

LEADING AUTHORITIES OF EUROPE AND AMERICA

EDITED BY

THOMAS L. STEDMAN, M.D.
NEW YORK CITY

IN TWENTY VOLUMES

VOLUME XVII.

INFECTIOUS DISEASES AND MALIGNANT NEW GROWTHS.

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DIPHTHERIA.

(GENERAL PATHOLOGY AND BACTERIOLOGY.)

BY

WILLIAM HALLOCK PARK,

NEW YORK.

DIPHTHERIA.

(GENERAL PATHOLOGY AND BACTERIOLOGY.)

HISTORY.

The specific contagious disease which we now call diphtheria can be traced back under various names to almost the Homeric period of Grecian history. The Greeks believed that it had been communicated to their country from Egypt. The description of the pharyngeal and laryngeal manifestation of this disease left by Aretæus leaves no doubt that it was of diphtheria that he wrote. Galen, in his remarks on the Chironion ulcer, tells us that the pseudomembrane was gotten rid of by coughing in the laryngeal form of the disease, and by hawking in the pharyngeal type. From time to time during the next one thousand years we hear of epidemics both in Italy and in other portions of the civilized world which indicate that the disease never absolutely ceased. In 1517 we read of a malignant form of the disease raging in Switzerland along the Rhine and in the Netherlands. In 1557 we read of further epidemics in France, Germany, Holland, and Spain. In Spain there was so great a mortality in 1613 that it was known as the diphtheria year. Heredia, in 1690, recognized the suffocative and asthenic types as well as the paralysis which occurs in the muscles of the soft palate, limbs, etc. The disease now crossed to America, and in the New England States we get clear accounts of its ravages. Thus Samuel Danforth in 1659 lost four of his eleven children within a fortnight by a "malady of the bladders in the windpipe."

In 1765 Home, a Scotchman, tried to show that "croup" and pharyngeal diphtheria were different diseases, and this subject remained under controversy until it was settled through bacteriological examinations that while most cases were undoubtedly diphtheria a few were not.

Bard, an American, supported in 1771 the opposite theory from Home, considering the process the same wherever located. In this ground he was much nearer to the facts than Home. His observations upon diphtheria were very important and accurate.

In 1821 Bretonneau published his first essay on diphtheria in Paris and gave to the disease its present name. His observations were so extensive and so correct that little advance in knowledge took place until the causal relations of the diphtheria bacilli and their associated microorganisms to the disease began to be recognized. Since then, the combined clinical, bacteriological, and pathological studies have sufficed to make diphtheria one of the best understood of diseases.

BACTERIOLOGY.

In the year 1883, bacilli which were very peculiar and striking in appearance were shown by Klebs to be of constant occurrence in the pseudomembranes from the throats of those dying of true epidemic diphtheria. One year later, Loeffler published the results of a very thorough and extensive series of investigations on this subject. He found the bacillus described by Klebs in many cases of throat inflammations which had been diagnosticated as diphtheria. He separated these bacilli from the other bacteria present and obtained them in pure culture. When he inoculated the bacilli upon the abraded mucous membrane of susceptible animals more or less characteristic pseudomembranes were produced, and frequently death or paralysis followed with characteristic lesions.

In 1887–88 further studies by Loeffler, Roux, and Yersin added to the poof of the dependence of diphtheria on this bacillus. It was found that, while no other forms of bacteria were constantly met with, the diphtheria bacilli were present in all characteristic cases of diphtheria, and that these bacilli possessed the morphological cultural and pathogenic qualities of those described by Klebs and Loeffler. The results of these investigations have since been confirmed by a great number of combined clinical and bacteriological observations both in animals and human beings. A very instructive accidental experiment was carried out under my observation some three years ago. One of the laboratory workers unintentionally drew quite a quantity of a bouillon culture of a virulent diphtheria bacillus into the throat, and two days later characteristic diphtheria of a serious type developed. All who have studied the bacteriology of diphtheria would now agree with the statement made by Welch that all the conditions have been fulfilled for diphtheria which are necessary to the most rigid proof of the dependence of an infective disease upon a given microorganism, viz., the constant presence of this organism in the lesions of the disease, the similar distribution of the organism in the experimental and in the natural disease, the isolation of the organism in pure culture, the reproduction of the essential lesions of the disease by inoculations with pure cultures, and the failure to produce this disease by any other bacteria. In view of these facts, we are now justified in saying that the name diphtheria, or at least primary diphtheria, should be applied, and exclusively applied, to that acute infectious disease usually associated with pseudomembranous affection of the mucous membranes which is primarily caused by the bacillus diphtheriæ of Loeffler.

Morphology.

When cover-glass preparations made from the cultures grown on blood serum are examined, the diphtheria bacilli are found to possess the following morphological characteristics: The diameter of the bacilli varies from 0.3 to 0.8 μ and the length from 1 to 6 μ. They occur singly and in pairs (see Figs. 6 and 7) and very infrequently in chains of three or four. The rods are straight or slightly curved, and usually are not uniformly cylindrical throughout their entire length, but are swollen at the end, or pointed at the ends and swollen in the middle portion. The average length of the bacilli in cultures from different sources frequently varies greatly and even from the same culture individual bacilli differ much in their size and shape. The two bacilli of a pair may lie with their long diameter in the same axis, or at an obtuse or an acute angle; or the pairs of bacilli may lie side by side or irregularly across each other. The bacilli possess no spores, but have in them highly refractile bodies.

The Klebs-Loeffler bacilli *stain* readily with ordinary aniline dyes and retain fairly well their color after staining by Gram's method. With an alkaline solution of methylene blue, the bacilli from blood-serum cultures especially, and from other media less constantly, stain in an irregular and extremely characteristic way (see Fig. 4). The bacilli do not stain uniformly. In many cultures round or oval bodies situated at the ends or in the central portions stain much more intensely than the rest of the bacillus. Sometimes these highly stained bodies are thicker than the rest of the bacillus; again they are thinner and surrounded by a more slightly stained portion. The bacilli seem to stain in this peculiar manner at a certain period of their growth, so that only a portion of the organisms taken from a culture at any one time will show the characteristic staining. In old cultures it is often difficult to stain the bacilli, and the staining, when it does occur, is frequently not at all characteristic. The same round or oval bodies which take the methylene blue more intensely than the remainder of the bacillus are brought out still more distinctly by the Neisser stain.

The Neisser stain is carried out by placing the cover-slip smear of diphtheria or other bacilli in solution No. 1 for from one to two seconds, and then, after washing, in No. 2 for from three to five seconds.

The bacilli will then appear either entirely brown or will show at one or both ends a dark blue round body. With characteristic diphtheria bacilli taken from a twelve to eighteen hours' growth on serum nearly all will show the blue bodies, while with the pseudo-type few if any will be seen.

The solutions are as follows:

No. 1.

Alcohol (ninety-six per cent.)	20 parts.
Methylene blue (Grübler)	1 part.
Distilled water	950 parts.
Acetic acid (glacial)	50 "

No. 2.

Bismarck brown	1 part.
Boiling distilled water	500 parts.

Neither the Neisser stain nor other stains, such as the modifications of the Roux stain, have in our hands given any more information as to the virulence of the bacilli than the usual methylene blue solution of Loeffler. Mitchell's modification of the Roux stain is as follows:

Dahlia, one-per-cent. aqueous solution,	1 part.
Methylene green, one-per cent. aqueous solution,	5 parts.
Water,	4 parts.

The morphology of the diphtheria bacillus varies considerably with the different culture media employed. On glycerin agar or simple nutrient agar it is smaller and as a rule more regular in form than when grown on other usual culture media. Short, spindle, lancet, or clubshaped forms, always segmented and staining uniformly, are here commonly observed. In bouillon the morphology of the organism is about intermediate, both in size and shape, between the forms seen on glycerin agar and those on blood serum. The bacilli which have developed in the pseudomembranes or exudate in cases of diphtheria resemble in shape those grown on blood serum but stain more evenly.

But though the morphology of the diphtheria bacillus is more regular under some circumstances than others, its chief morphological characteristic is its irregularity of form.

Biology.

The Klebs-Loeffler bacillus is non-motile and non-liquefying. It is *aërobic.* It grows most readily in the presence of oxygen, but also without it; it is thus *facultative anaërobic.* It does not form spores. Its thermal death point with ten minutes' exposure is 58° C. and with longer exposure a lower temperature. In the dry state diphtheria

PLATE I.

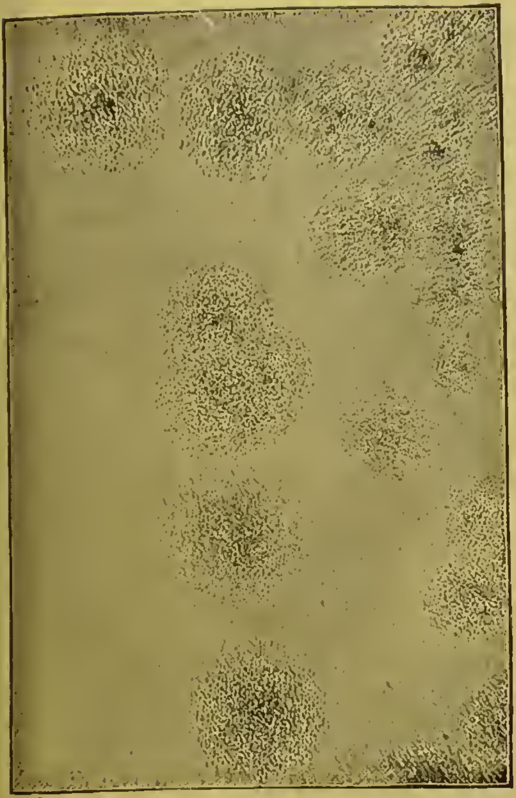

FIG. 1.—Colonies of Diphtheria Bacilli on Agar. × 120 diameters.

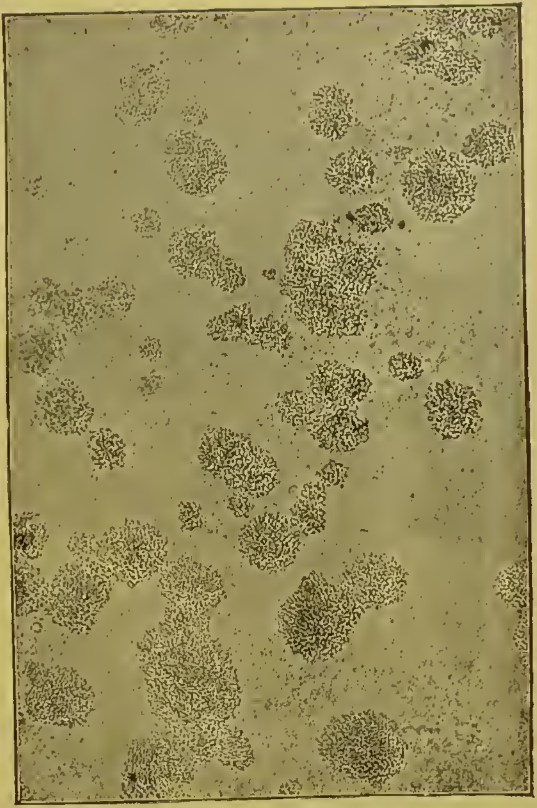

FIG. 2.—Colonies of Pseudodiphtheria Bacilli. × 120 diameters.

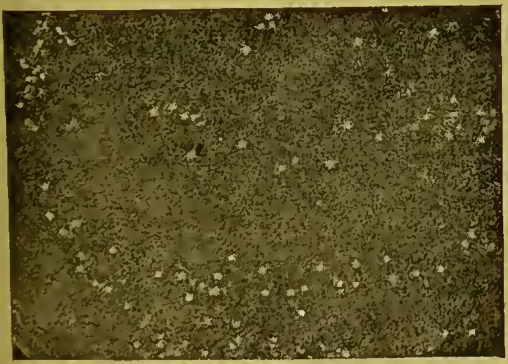

FIG. 3.—Colonies of Diphtheria Bacilli on Agar. Actual size after eighteen hours' growth.

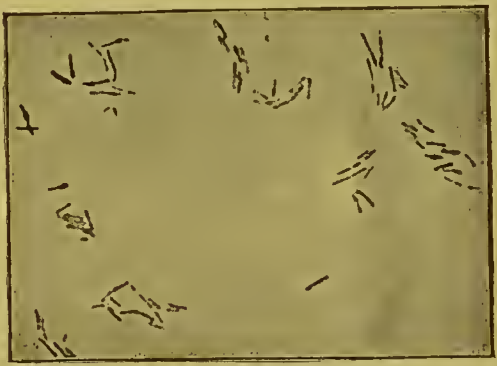

FIG. 4.—Characteristic Diphtheria Bacilli, showing irregularity of form and staining.

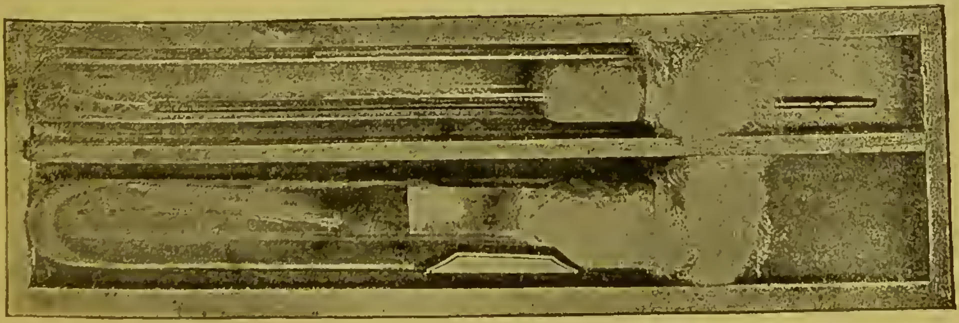

FIG. 5.—Culture Outfit. Box, sterile swab, and tube of blood serum.

PLATE II.

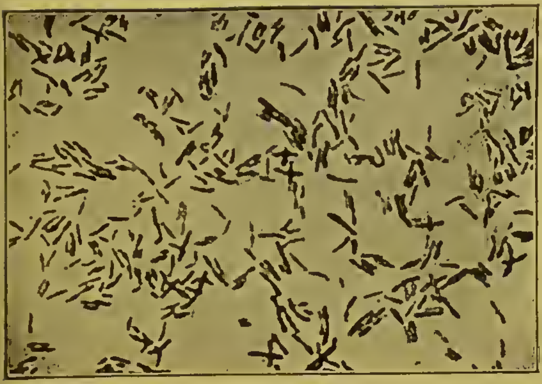

Fig. 6.—Diphtheria Bacilli, showing irregular form, but unusually even staining. Many xerosis bacilli have a similar appearance.

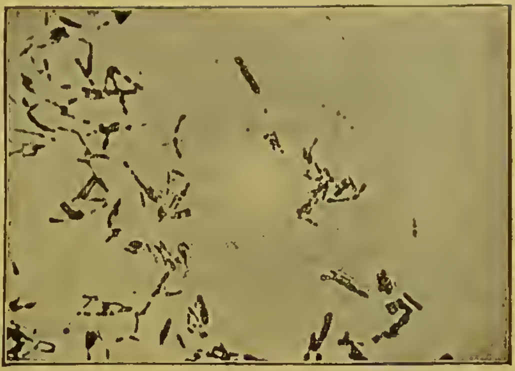

Fig. 7.—Characteristic Diphtheria Bacilli, showing very long and irregular forms.

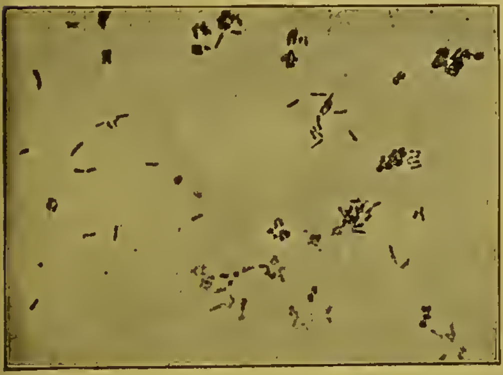

Fig. 8.—Pseudodiphtheria Bacilli with a few Diplococci.

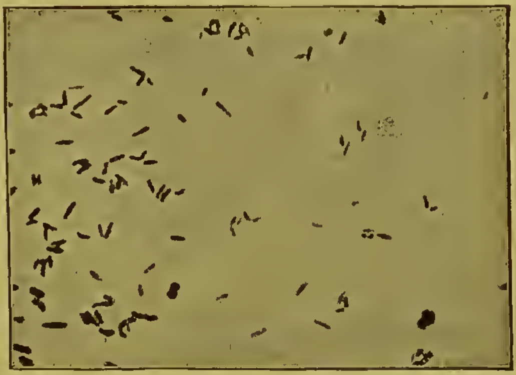

Fig. 9.—Pseudodiphtheria Bacilli with a few Diplococci.

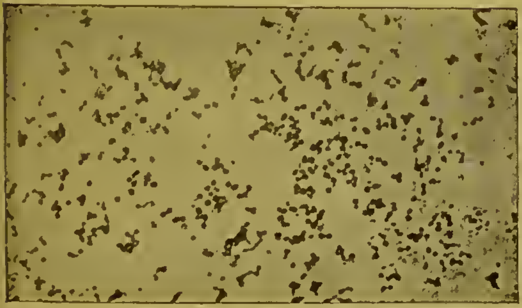

Fig. 10.—Steptococci and Diplococci from a Culture Growth on Blood Serum from a Case of Pseudodiphtheria.

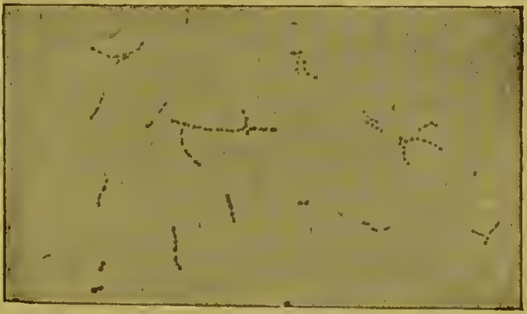

Fig. 11.—Steptococci and Diplococci as seen in a Smear made directly from the Exudate in a Case of Pseudodiphtheria.

bacilli may live for weeks or months. Thus I found scrapings from a dry bit of membrane to contain vigorous living bacilli for a period of four months after removal from the throat, and I believe if the membrane had not been at that time completely used, living bacilli could have been obtained for a much longer period; in culture media when kept at the blood heat they usually die after a few weeks or months, but under certain conditions, as when sealed in tubes and protected from heat and light, they retain their virulence for years. The bacillus is not sensitive to cold under ordinary conditions, and retains its virulence after freezing. It begins to develop, but grows slowly, at a temperature of 20° C., or even less. It grows more rapidly as the temperature rises, and attains its maximum development at 37° C. It may grow at a temperature as high as 41° C. and retain its virulence for months.

Growth on Blood Serum.—Loeffler's blood-serum mixture (see p. 37) is the most favorable medium for the growth of the diphtheria bacillus, and is used particularly for diagnostic purposes in examining cultures from the throats of persons suspected of having diphtheria. If we examine the growth of the diphtheria bacillus in pure culture on blood serum, we shall find at the end of from ten to twelve hours small colonies of bacilli, which appear as pearl-gray, whitish-gray, or more rarely yellowish-gray slightly raised points. The colonies when separated from each other may increase in forty-eight hours so that the diameter may be one-eighth of an inch. The borders are usually somewhat uneven. The colonies lying together become confluent and fuse into one mass, especially if the serum be rather moist. During the first twelve hours, the colonies of the diphtheria bacilli are about equal in size to those of the other pathogenic bacteria which are often present in the throat; but after this time the diphtheria colonies become larger than those of the streptococci and smaller than those of the staphylococci. The diphtheria bacilli in their growth never liquefy the blood serum.

Growth on Agar.—On one per cent. slightly alkaline plain nutrient or glycerin agar the growth of the diphtheria bacillus is less certain and luxuriant than upon blood serum; but the appearance of the colonies when examined under a low-power lens, though very variable, is often far more characteristic. The diphtheria bacillus obtained from old laboratory cultures grows well as a rule on suitable nutrient or glycerin agar, but when fresh from pseudomembrane it frequently grows on these media with great difficulty, and the colonies develop so slowly as to be covered up by the more luxuriant growth of other bacteria, or fail to develop at all. Since the growth of some of the associated bacteria in pseudomembranes produces acid in the media, this fact should be taken into consideration; and if such cultures are made on agar, it should be rendered somewhat more alkaline than is absolutely necessary for the best growth of the diphtheria bacilli.

If the colonies develop deep in the substance of the agar, they are usually round or oval, and, as a rule, present no extensions; but if near the surface, commonly from one but sometimes from both sides they spread out an apron-like extension which exceeds in surface area the rest of the colony. When the colonies develop entirely on the surface, they are more or less coarsely granular, and usually have a dark centre and vary very much in their thickness. Some are almost translucent; others are thick and almost as luxuriant as the staphylococcus. The edges are sometimes jagged and frequently shade off into a delicate lace-like fringe; at other times the margins are more even and the colonies are nearly circular. With a high-power lens the edges show sprouting bacilli. The colonies are gray or grayish-white by reflected light and pure gray with an olive tint by transmitted light (see Figs. 1 and 3).

The growth of the diphtheria bacillus upon agar presents certain peculiarities which are of the utmost practical importance. If a large number of the bacilli from a recent culture are implanted upon a properly prepared agar plate, a certain and fairly vigorous growth will always take place. If, however, the agar is inoculated with an exudate from the throat which contains but few bacilli, no growth whatever may occur, while the tubes of coagulated blood serum inoculated with the same exudate contain the bacilli abundantly, those which have not become accustomed to bouillon media growing better on blood serum. Again, agar prepared from broth made from different specimens of beef, or to which different peptones have been added, varies somewhat as to its suitability for the growth of the bacilli. Because of the uncertainty, therefore, of obtaining a growth by the inoculation of agar with bacilli unaccustomed to this medium, or with bacilli of diminished vigor, agar is a far less reliable medium than blood serum for use in cultures for diagnostic purposes. If used for this purpose, the agar should at least be tested by means of a pure culture of the diphtheria bacillus before being employed experimentally. Nutrient plain or glycerin agar is, however, the medium employed to get by plating methods a pure culture from the original serum tube. The agar should be freshly melted and poured in the Petri dish for this purpose. After it has hardened, a number of plates are streaked across with bacilli from colonies on the serum culture, which appear in size and color like the diphtheria bacilli. Other plates are made from a general mixture of all the bacteria selected as a rule from the drier portion of the serum. The plates are left in the incubator for twelve hours at 37° C. In the examination of the plates one should first seek for typical colonies and then later for any that look nearest the characteristic picture. Diphtheria colonies are very apt to be found at the edges of the streaks of bacterial growth.

Growth in Bouillon.—The diphtheria bacillus also grows readily in slightly alkaline broth with or without the addition of a small amount of glucose. The characteristic growth in neutral bouillon is one showing fine grains. These deposit along the sides and bottom of the tube, leaving the broth nearly clear. A few cultures in neutral bouillon and many in alkaline bouillon produce for twenty-four or forty-eight hours a more or less diffuse cloudiness, and frequently a film forms over the surface of the broth. On shaking the tube this film breaks up and slowly sinks to the bottom. The diphtheria bacillus in its growth causes a fermentation of the meat sugars and the glucose and thus changes the reaction of the bouillon, rendering it distinctly less alkaline within forty-eight hours, and then after a variable time more alkaline again through the fermentation of other substances.

Growth on Gelatin.—The growth on this medium is much slower, more scanty, and less characteristic than that on the other media mentioned, on account of the lower temperature at which it is used. The colonies of the diphtheria bacillus on gelatin are not large; when deep down in the substance of the gelatin they are granular in structure, having a dark centre and one or more transparent zones arranged concentrically around this. The periphery is irregular.

Growth on Potato.—On this medium the growth is slow, not characteristic, described as an "invisible growth," but nevertheless present as a thin dry glaze near the point of inoculation.

Growth in Milk.—The diphtheria bacillus grows readily in milk and, according to Sternberg, at a comparatively low temperature (20° C.). Thus milk having become inoculated with the diphtheria bacillus may under certain conditions be the means of conveying infection to previously healthy persons. Though this growth takes place, the milk remains unchanged in appearance.

Pathogenesis.

The diphtheria bacillus is pathogenic for guinea-pigs, rabbits, chickens, pigeons, small birds, and cats; also in a lesser degree for dogs, goats, cattle, and horses, but not for rats and mice. In all these animals the disease is caused by the poison produced and given off by the living bacilli, not by their simple mechanical presence in the tissues.

The virulence of diphtheria bacilli from different sources varies enormously. Thus .002 c.c. of a forty-hour bouillon culture of one bacillus will kill a guinea-pig, which it would require 1 c.c. of the culture of another bacillus to kill. The same marked variation occurs in the amount of toxin produced by different bacilli in their growth in media outside of the body. There are also bacilli which have no virulence whatever of a specific nature. Moreover, the diphtheria bacilli differ greatly in the tenacity with which they retain their virulence when grown outside the body. The bacillus that we have used in the laboratory of the Board of Health has retained its virulence almost unaltered for four years in bouillon cultures. Other bacilli have lost fifty per cent. of their virulence, after being kept only a few months. The passage of diphtheria bacilli through the bodies of susceptible animals does not increase their virulence to any considerable extent, this being probably due to the fact that the bacilli multiply but little in the tissues.

At the autopsy of animals dying from the poisons produced by the bacilli, the characteristic lesions described by Loeffler are found. At the seat of inoculation there is a grayish focus surrounded by an area of congestion; the subcutaneous tissues for some distance around are œdematous; the adjacent lymph nodes are swollen; and the serous cavities, especially the pleura and the pericardium, frequently contain an excess of fluid, usually clear, but at times turbid; the lungs are generally congested. If the organs are subjected to microscopical examination, the lesions described by Welch and Flexner, Babes, and others are found. There are numerous smaller and larger masses of necrotic cells, which are permeated by leucocytes. The heart and voluntary muscular fibres usually show degenerative changes. Occasionally there is fatty degeneration of the liver and kidneys. The number of leucocytes in the blood is increased. From the area surrounding the point of inoculation virulent bacilli may be obtained, but in the internal organs they are only occasionally found, unless an enormous number of bacilli have been injected. Paralysis, commencing usually in the posterior extremities and then gradually extending to the whole body and causing death by paralysis of the heart or respiration, is also produced in many cases in which the inoculated animals do not succumb to a too rapid intoxication. In rare instances, the muscles of the neck or of the larynx are first paralyzed, and thus characteristic symptoms are caused. In a number of animals I have seen recovery take place three to six weeks after the onset of the paralysis. The occurrence of these paralyses, following the introduction of the Klebs-Loeffler bacilli, completes the resemblance of the experimental disease to the natural malady in man.

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Diphtheria Toxin.

It is evident that a microorganism which, when injected subcutaneously, destroys the life of susceptible animals and produces such marked anatomial changes in the internal organs, while it is found only at or near the point of inoculation, must owe its pathogenic power to the formation of a poison which, being absorbed, gives rise to toxæmia and death. This poison or *toxin* has been isolated by Roux and Yersin, Brieger, Fraenkel, and others, by filtration through porous porcelain from cultures of the living bacilli. It has not yet been successfully analyzed, so that its chemical composition is unknown, but it has many of the properties of certain of the globulins, being precipitated by the same substances and destroyed by the same degree of heat and by the same chemical agents, and appears to be analogous to the poisons of certain venomous serpents.

The Artificial Production of Toxin.—The artificial production of toxin in cultures of the diphtheria bacillus has been found to depend upon definite conditions which are of practical importance. The researches of Roux and Yersin laid the foundation of our knowledge. Their investigations have been continued by Theobald Smith, Spronck, ourselves (Park and Williams), and others. After an extensive series of investigations we came to the following conclusions: Toxin is produced by virulent diphtheria bacilli at all times during their life when the conditions are favorable. Under less favorable conditions some bacilli are able to produce toxin, while others are not, or it may be that some conditions favor some bacilli while they are deleterious to others obtained from a different source. Diphtheria bacilli may find the same conditions suitable for luxuriant growth, but unsuitable for the production of toxin. The requisite conditions for the best development of toxin, as judged by the behavior of a number of cultures, are a temperature from about 35° to 37.5° C., a slight alkalinity, which should be from 6 to 10 c.c. of normal soda solution per litre above the neutral point to litmus, suitable peptone and meat for the preparation of the nutrient bouillon, and a duration of growth of the culture of from five to eight days, according to the peculiarities of the culture employed. At a too early period toxin has not sufficiently accumulated, at a too late period it has degenerated. In our experience the amount of sugar present in the meat is of minor importance, at least this is true for the varieties of beef in New York, so long as the bouillon has been made sufficiently alkaline to overcome the acid produced by the fermentation of the sugar through the products of the bacilli. In neutral bouillon, as pointed out by Smith and Spronck, the sugar does produce sufficient acid to interfere with the growth of the bacilli and the development of toxin. This can be prevented by the previous destruction of the sugar through the fermentation caused by the growth of the bacterium coli or other bacteria having similar action. Besides the sugar in the meat there are other substances, whose nature is unknown, which hinder a full growth of the bacilli or production of toxin. This is true of bouillon made directly from fresh meat, old meat, fermented meat, or meat extracts.

Under the best conditions we can devise, toxin begins to be produced by bacilli from some cultures when freshly sown in bouillon some time during the first twenty-four hours; from other cultures, for reasons not well understood, not for two to four days. The greatest accumulation of toxin is on the fourth day, on the average, after the production of toxin has commenced. After that time the number of living bacilli rapidly diminishes in the culture and the conditions for those remaining alive are not suitable for the rapid production of toxin. As the toxin is not stable, the deterioration taking place in the toxin already produced is greater than the amount of new toxin still forming.

The relations of toxin to antitoxin will be described after the subject of antitoxin has been considered.

Non-Virulent Diphtheria. Xerosis Bacilli.

In the very large number of tests for virulence of the bacilli obtained from hundreds of cases of suspected diphtheria, which have been carried out during the past four years in the laboratories of the Health Department of New York City, in over ninety-five per cent. of cases the bacilli derived from exudates or pseudomembranes and possessing the characteristics of the Loeffler bacilli have been found to be virulent. But there is associated with the virulent bacilli in pseudomembranous affections occasionally a bacillus, morphologically and in its behavior on culture media identical with the Klebs-Loeffler bacillus, though it produces, at least in artificial culture media and the usual test animals, no appreciable diphtheria toxin. In accordance with Roux and Yersin we believe this bacillus should be considered as an attenuated variety of the diphtheria bacillus which has lost its power to produce diphtheria toxin; these observers, and others following them, having shown that the virulent bacilli can be artificially attenuated by cultivating them at a temperature of 39.5° to 40° C. in a current of air. It is also well known to all bacteriologists that diphtheria bacilli of identical shape, size, and staining peculiarities, but of very different degrees of virulence, are often found in one and the same individual during the course of a case of diphtheria and still more frequently in different cases. In our experience some cultures hold their virulence even when grown at 41° C. for a number of months, while others lose it more quickly. Bacilli are also found which resemble diphtheria bacilli very closely except in toxin production, but differ in one or more particulars. Both these and the characteristic non-virulent bacilli are found occasionally upon all the mucous membranes, both when inflamed and when apparently normal. From their having been found in a number of cases of the condition known as xerosis conjunctivæ by Kuschbert and Neisser, these bacilli are often called xerosis bacilli. Under this name different observers have placed bacilli identical with the diphtheria bacilli and others differing quite markedly from them. The bacilli may be almost non-pathogenic in guinea-pigs or they may kill, as we have found in a number of instances, in doses of 2 to 5 c.c. hypodermically injected. Animals are not protected by diphtheria antitoxin from the action of these bacilli.

LOCATION OF DIPHTHERITIC INFLAMMATIONS AND VIRULENCE OF BACILLI.

Virulent bacilli are found not only in pseudomembranous angina of the fauces, larynx, and nasal cavities, but also occasionally in membranous affections of the skin, vagina, rectum, conjunctiva, nose, and ear (simple membranous rhinitis and otitis media). From the severity of an isolated case the virulence of the bacilli cannot be accurately determined. The most virulent bacillus I have seen with was obtained from a mild case of diphtheria simulating tonsillitis. Another case, however, infected by this bacillus proved to be very severe. In localized epidemics the average severity of the cases probably indicates roughly the virulence of the bacillus causing the infection, as here the individual susceptibility of the different persons infected would, in all likelihood when taken together, be similar to that of other groups; but even in this instance special conditions of climate, food, or race may influence certain localities. Moreover, the bacteria associated with the diphtheria bacilli, and which are liable to be transmitted with them, may influence the severity of and the complications arising in the cases.

VIRULENT BACILLI IN HEALTHY THROATS.

Virulent bacilli have frequently been found in healthy throats of persons who have been brought in direct contact with diphtheria patients or infected clothing without contracting the disease. It is therefore apparent that infection in diphtheria, as in other infectious diseases, requires not only the presence of virulent bacilli, but also a susceptibility to the disease, which may be inherited or acquired. Among the predisposing influences which contribute to the production of diphtheritic infection may be mentioned the breathing of foul air and living in overcrowded and ill-ventilated rooms, poor food, certain diseases, more particularly catarrhal inflammations of the mucous membranes, and depressing conditions generally. Under these conditions an infected mucous membrane may become susceptible to disease. Park and Beebe (1894) report that, in the examination of the throats of 330 healthy persons who had not come in contact, so far as known, with diphtheria, the presence of virulent bacilli was demonstrated in 8 only, 2 of whom later developed the disease. In 24 of the 330 healthy throats non-virulent or attenuated forms of the diphtheria bacillus were found. Very similar observations have been made by others in many widely separated countries.

The Persistence of Diphtheria Bacilli in the Throat.—The continued presence of virulent diphtheria bacilli in the throats of patients who have recovered from the disease, and after the disappearance of the exudate, has been repeatedly demonstrated. In 2,566 cultures Park and Beebe found that in 304 of 605 consecutive cases the bacilli disappeared within 3 days after the disappearance of the pseudomembrane; in 176 cases they persisted for 7 days; in 64 cases for 12 days, in 36 cases for 15 days, in 12 cases for 3 weeks, in 4 cases for 4 weeks, and in 2 cases for 9 weeks.

Pseudodiphtheria Bacilli.

Besides the typical bacilli which produce diphtheria toxin and those which do not, but which, so far as we can determine, are otherwise identical with the Loeffler bacillus, there are other bacilli found in positions similar to those in which diphtheria bacilli abound, which, though resembling these organisms in many particulars, yet differ from them as a class in others equally important. These bacilli are rather short, plump, and more uniform in size and shape than the true Loeffler bacillus (Figs. 8 and 9). The great majority of them in any culture show no polar granules with the Neisser stain and stain evenly throughout with the alkaline methylene blue solution. They produce alkali only, instead of at first both acid and alkali in their growth in bouillon containing glucose. They are found in varying abundance in different localities in about one per cent. of the normal throat and nasal secretions, in New York City, according to Park and Beebe, and seem to have now at least no connection with diphtheria; whether they were originally derived from diphtheria bacilli is doubtful. They never produce diphtheria toxin, and to them properly has been applied the name *pseudodiphtheria bacilli.* It may be added here that no facts have come to light which indicate that bacilli which do not produce diphtheria toxin in animals ever produce it in man. It must also be borne in mind, however, that such proof is necessarily very difficult to obtain.

Mixed Infection in Diphtheria.

These different bacilli, however, are not the only bacteria present in human diphtheria. Various cocci, more particularly streptococci, staphylococci, and pneumococci, are almost always found associated with Loeffler bacilli in diphtheria, playing an important part in the disease and leading often to serious complications (sepsis and bronchopneumonia). Indeed, the prognosis in a case of diphtheria is now judged to be graver, other things being equal, according as the disease runs its course with or without the accompaniment of septic infection. These cases of so-called *mixed infection* in diphtheria have within recent years attracted considerable attention, and have been the subject of a number of animal experiments. Though the results of these investigations so far have been somewhat indefinite, they would seem to indicate that when other bacteria are associated with the diphtheria bacilli they mutually assist one another in their attacks upon the mucous membrane, the streptococcus being particularly active in this respect, often opening the way for the invasion of the Loeffler bacillus into the deeper tissues or supplying needed conditions for the development of its toxin. Thus diphtheria is not always a primary, but often a secondary, disease, following on some other infection, as measles or scarlet fever. In most fatal cases of bronchopneumonia following laryngeal diphtheria we find not only abundant pneumococci or streptococci in the inflamed lung areas, but also in the blood and tissues of the organs. As these infections are in no way influenced by the diphtheria antitoxin they frequently are the cause of the fatal termination.

False Diphtheria.

The pseudomembranous angina accompanying scarlet fever, and to a less extent other diseases, may not show the presence of diphtheria bacilli, but only the pyogenic cocci, especially streptococci. This is an important fact and one worthy of note, because it proves the existence of anatomical diphtheria which is not due to the Loeffler bacillus. The deposit covering the inflamed tissues in these non-specific cases is, it is true, rather an exudate than a true pseudomembrane. The majority of these cases, however, are mild affections which seldom result in death; while, on the other hand, it has been found, in almost every case of fatal diphtheria (with the exception of scarlatinal diphtheria), that the pseudomembrane taken on autopsy contained virulent diphtheria bacilli. The bacteria which occur in *false diphtheria* are streptococci, staphylococci, diplococci (Figs. 10 and 11), and sometimes pseudodiphtheria bacilli or bacilli which are morphologically and culturally distinct from the Loeffler bacilli.

The Transmission of Diphtheria.

The possibility of the transmission of diphtheria from animals to man cannot be disputed for cats and many animals can be infected, but there are no authentic cases of such transmission on record. So-called diphtheritic disease in animals and birds is usually due to other microorganisms than the diphtheria bacilli. Diphtheritic infection, however, can generally be traced, directly or indirectly, to its source; though there are undoubtedly some cases of diphtheria in which we cannot determine the source of the infection. We believe, nevertheless, that diphtheria is never spontaneous.

Let us consider some of the means by which the disease may be communicated. In actual experiment, the Loeffler bacillus has been found to live for weeks and months, namely, by Hoffmann on blood serum for one hundred and fifty-five days; by Loeffler and Park for seven months; and by Klein in gelatin for eighteen months. The bacilli have been observed to remain virulent in bits of dried membrane by Loeffler for fourteen weeks, by Park for seventeen, and by Roux and Yersin for twenty weeks. Dried on silk threads Abel reports that they may sometimes live for one hundred and seventy-two days, and upon a child's plaything which had been kept in a dark place they lived for five months. The virulent bacilli have been found on soiled bedding or clothing of a diphtheria patient, on drinking-cups, shoes, hair, slate pencils, etc. Beside these sources of infection by which the disease may be indirectly transmitted, virulent bacilli may be directly received from the pseudomembrane, exudate, or discharges of diphtheria patients; from the secretions of the nose and throat of convalescent cases of diphtheria in which the virulent bacilli persist; and from the healthy throats of individuals who acquired the bacilli from being in contact with others having virulent germs on their persons or clothing. In such cases, the bacilli may sometimes live and develop for days or weeks in the throat without causing any lesion. When we consider that it is only the severe types of diphtheria that remain isolated during their actual illness, the wonder is, not that so many, but that so few persons contract the disease.

Susceptibility to and Immunity against Diphtheria.

An individual susceptibility to diphtheria, as in all infectious diseases, is necessary to contract this disease. Moreover, the diphtheria poison does not produce the same effect on the mucous membranes of all persons. Age has long been recognized to be an important factor in diphtheria. Children within the first six months of life are but little susceptible, the greatest degree of susceptibility being between the third and the tenth year, while adults are almost immune. An inherited susceptibility or "family predisposition" to the disease has also been observed.

Long before the discovery of the Klebs-Loeffler bacillus it was a well-known fact that two attacks of diphtheria seldom occurred in the same individual within short periods of time. To what this susceptibility or immunity is due is still only partially understood, but when we remember that simply a slight increase in the acidity or alkalinity of the bouillon in which the diphtheria bacilli is producing its toxin will prevent further production, it is easy to imagine that many changes in the throat secretion or in its mucous membrane may prevent the production by the bacillus of its toxin and therefore of its disease-producing power. But, as the result of animal experiments, it is now known that an artificial immunity against diphtheria can be produced, at least for a considerable length of time. By the inoculation of virulent or somewhat attenuated cultures or of diphtheria toxin Fraenkel, Behring, Wernicke, Aronson, Roux, and since then many others have succeeded in immunizing animals. But the most important and valuable results are those which have been obtained by Behring, in conjunction with others, who showed that the blood of immune animals contains a substance which neutralizes the diphtheria toxin. The blood serum of persons who have recovered from diphtheria has been found also to possess this protective property, which it acquires about a week after the beginning of the disease, and loses again in a few months. Moreover, the blood serum of many individuals, usually adults, who have never had diphtheria often has a slight general antitoxic property.

Antitoxic Serum.

The knowledge derived from these remarkable investigations into the protective powers of the blood serum of immunized animals has been employed with the most brilliant results for the treatment of diphtheria in man. The discovery of the method of the production of antitoxic serum or antitoxin in animals, and its practical application to the treatment and cure of diphtheria, has been shared by many experimenters, at first chiefly in Germany and France, and later in this country. Among those whose labors in this direction have rendered them most worthy of mention are Behring, Ehrlich, Boer, Kossel, and Aronson, in Germany; Roux, Martin, and Chaillon, in France.

Results of the Antitoxin Treatment of Diphtheria.—Though the results of the antitoxin treatment in diphtheria belong properly to the province of serumtherapy rather than to bacteriology, in view of the great practical importance of the subject it may not be amiss to quote here the conclusions arrived at by Biggs and Guerard after a review of all the statistics and opinions published since the beginning of the antitoxin treatment in 1892.

"It matters not from what point of view the subject is regarded if the evidence now at hand is properly weighed, but one conclusion is, or can be reached—whether we consider the percentage of mortality from diphtheria and croup in cities as a whole, or in hospitals, or in private practice; or whether we take the absolute mortality for all the cities of Germany whose population is over 15,000, and all the cities of France whose population is over 20,000; or the absolute mortality for New York City, or for the great hospitals in France, Germany, and Austria; or whether we consider only the most fatal cases of diphtheria, the laryngeal and operative cases; or whether we study the question with relation to the day of the disease on which treatment is commenced, or the age of the patient treated; it matters not how the subject is regarded or how it is turned for the purpose of comparison with previous results, the conclusion reached is always the same, namely, there has been an average reduction of mortality from the use of antitoxin in the treatment of diphtheria of not less than fifty per cent., and under the most favorable conditions a reduction to one-quarter, or even less, of the previous death rate. This has occurred not in one city at one particular time, but in many cities, in different countries, at different seasons of the year, and always in conjunction with the introduction of antitoxin serum and proportionate to the extent of its use."

THE PRODUCTION OF DIPHTHERIA ANTITOXIN FOR THERAPEUTIC PURPOSES.

As a result of the work of years in the laboratories of the Health Department of New York City, the following may be laid down as a practical method.

The strongest diphtheria toxin possible should be obtained by taking a very virulent culture and growing it under the conditions described in the section on toxin (p. 15). The culture after a week's growth is removed, and having been tested for purity is rendered sterile by the addition of ten per cent. of a five-per-cent. solution of carbolic acid. On the following day the sterile culture is filtered through ordinary sterile filter paper and stored in full bottles in a cold place until needed.

The horses used should be young, vigorous, of fair size, and absolutely healthy. Vicious habits, such as kicking, etc., make no difference, of course, except to those who handle the animals. A number of such horses are severally injected with an amount of toxin sufficient to kill ten thousand guinea-pigs of 250 gm. weight (about 40 c.c. of strong toxin). With each injection of toxin ten thousand units of antitoxin are given. After from three to five days, so soon as the fever reaction has subsided, a second subcutaneous injection of a slightly larger dose is given. At intervals of from five to ten days increasing injections of pure toxin are made, until at the end of two months from ten to twenty times the original amount is given. The horses are now bled and the blood serum is tested for antitoxin. Those having an antitoxin containing less than two hundred units in each cubic centimetre are discarded. The remaining horses receive steadily increasing doses, the rapidity of the increase and the interval of time between the doses (about a week) depending somewhat on the reaction following the injection, an elevation of temperature of more than 3° F. being undesirable. At the end of three months the antitoxic serum should contain from three hundred to eight hundred units in each cubic centimetre, according to the horse used. The best horses continue to furnish high-grade antitoxin for years. Each year they should be given an interval of three months' freedom from inoculations.

In order to obtain the serum the blood is withdrawn from the jugular vein by means of a sharp-pointed cannula which is plunged through the vein wall, a slit having been made in the skin. The blood is received in large Erlenmeyer flasks and allowed to clot, the flasks being placed at first, while clotting is taking place, in a slanting position. The serum is siphoned off by means of aseptic glass and rubber tubing, and is stored in large flasks. From this, as needed, small phials are filled. The phials and their stoppers, as indeed all the utensils used for holding the serum, must be absolutely sterile, and every possible precaution must be taken to avoid contamination of the serum. An antiseptic may be added to the serum as a preservative, but it is not necessary and probably inadvisable.

Antitoxin is a substance which we know only from its physiological side. It has never been obtained in pure form—in fact it cannot be chemically separated from the toxin. It is a proteid substance destroyed by heat above 55° C., and is precipitated from its solutions by the same substances as some of the globulins. Kept from access of air and light and in a cold place it is fairly stable, deteriorating not more than fifty per cent. and often not at all within a year.

Diphtheria antitoxin has the power of neutralizing diphtheria toxin, so that when a certain amount is injected into an animal before or together with the toxin it overcomes its poisonous action. Whether this is a direct chemical combination between the antitoxin and the toxin, as assumed by Ehrlich, or whether the antitoxin has some specific protective influence on the cells of the body, we do not know.

This power possessed by a definite quantity of antitoxin to neutralize a certain amount of toxin is utilized in testing antitoxin. Guinea-pigs of 250 gm. weight are infected with one hundred or with ten fatal doses of toxin which has been previously mixed with an amount of antitoxin believed to be sufficient to protect from the toxin. If the guinea-pig lives four days, but dies soon after, the amount of antitoxin is 1 or .1 according as one hundred or ten fatal doses were employed.

Until within a fairly recent time the filtered or sterilized bouillon in which the diphtheria bacillus had grown and produced its "toxin" was supposed to require for its neutralization an amount of antitoxin directly proportional to its toxicity as tested in guinea-pigs. Thus, if from one bouillon culture ten fatal doses of "toxin" were required to neutralize a certain quantity of antitoxin, it was believed that ten fatal doses from every culture, without regard to the way in which it had been produced or preserved, would also neutralize the same amount of antitoxin. Upon this belief was founded the Behring-Ehrlich definition of an antitoxin unit.

The results of tests by different experimenters with the same antitoxic serum, but with different diphtheria toxins proved this opinion to be incorrect. Ehrlich ("Die Wertbemessung des Diphtherieheilserums und deren theoretische Grundlagen," *Klinisches Jahrbuch*, 1897) deserves the credit for first clearly perceiving and publishing this. He obtained from various sources twelve toxins and compared their neutralizing value upon antitoxin; these tests gave most interesting and important information. The results in six toxins, which are representative of the twelve, are as shown in Table I.

From the facts set forth in the tables Ehrlich has derived interesting theories, which, if true, would add greatly to our knowledge of toxins, and would also have a very direct influence upon the present methods of standardizing antitoxin. He believes that the diphtheria bacilli in their growth produce toxin which, so long as it remains chemically unaltered, has a definite poisonous strength with a definite value in neutralizing antitoxin. This neutralization he believes to be a chemical union, in which two hundred fatal doses of toxin for a 250 gm. guinea-pig combine with one unit of antitoxin. The toxin is, however, an unstable compound and begins to change almost immediately into substances which are not, at least acutely, poisonous, but which retain their full power to neutralize antitoxin. These substances, according to Ehrlich, fall into three groups. The first has more affinity for combining with the antitoxin than the toxin itself (protoxoids). The second has the same affinity (syntoxoids). The third has less affinity (epitoxoids).

TABLE I.—(FROM EHRLICH.)

Toxin specimen number of Ehrlich.	Estimated "minimal" fatal dose for 250 gm. guinea-pigs.	Smallest number of fatal doses of toxic bouillon required to kill a 250-gm. guinea-pig within five days when mixed with one antitoxin unit. "L_+" Ehrlich.	Fatal doses required to "completely neutralize one antitoxin unit" as determined by the health of the guinea-pig remaining unaffected. "L_0" Ehrlich.	$L_+ - L_0$	Data upon "toxin" specimen given by Ehrlich.
2	0.03	42	32	10	Preserved two years.*
4	0.009	39.4	33.4	6	Old, deteriorated from .003 to .009.
7	0.0165	76.3	54.4	22	Fresh toxin, preserved with tricresol.
9	0.039	123	108	15	A number of fresh cultures grown at 37° C. four and eight days.
10	0.001	29.2	27.5	1.7	Precipitated from greatly deteriorated "toxin."
12	0.0025	100	50	50	Tested immediately after its withdrawal.

According to him, if a mixture of toxoids and toxin is added to antitoxin, the protoxoids first combine with the antitoxin, then the syntoxoids and the toxin combine in equal proportions, so long as the supply lasts, with the amount of antitoxin remaining or, if there is a surplus, with enough to satisfy them; finally, if any antitoxin remains, the epitoxoids unite with it.

If to a mixture, in which all three toxoids as well as toxin have united with antitoxin, some additional toxic culture bouillon be added, the new protoxoids displace first the epitoxoids and then, if free protoxoids remain, the toxin and the syntoxoids from their antitoxin, and thus liberate as well as add free toxin to the solution.

Ehrlich states as an important law that toxin molecules change into toxoid molecules either by three toxin molecules becoming two toxoid and one toxin molecules, or by two toxin molecules changing into one toxoid and one toxin molecule.

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* For number 9 only does Ehrlich give the duration of the culture growth in the incubator by which the toxin was produced.

The practical conclusion which he draws is that from the absolute amount of poison in a given quantity of bouillon alone, nothing can be determined as to its neutralizing value for antitoxin, and that, therefore, the old Behring-Ehrlich method must be greatly modified; namely, that in any bouillon we must determine not only the amount of toxin but also of toxoids before we can judge of its neutralizing value. This he believes he can accurately accomplish.

He gives an interesting theory to explain the production of antitoxin in the blood. This he does upon the supposition that, when absorbed, the toxin combines with a portion of certain selected cells, and that this portion by its union with toxin becomes, at least physiologically, dead. The cell replaces this dead matter with new and similar substance; after several repeated losses and replacements of this substance the cells produce it in excess. This substance, whether originally in the normal cell or reproduced there, and whether remaining in the cell or thrown out into the circulation, is antitoxin.

Ehrlich attempts to separate each culture bouillon into its constituent toxoids and toxin by a formula worked out by him. He believes that his investigations show that the total amount of pure toxin which neutralizes one unit of antitoxin is 200 minimal fatal doses, and that in ordinary culture fluids, which are mixtures of toxoids and toxin, an antitoxin unit neutralizes 200 fatal doses of toxin minus the number of toxin molecules changed into toxoid molecules. Letting $A =$ number of toxin molecules, and $Z =$ epitoxoids, then one unit of antitoxin fully neutralized equals $(200-A-Z)$ toxoid antitoxin $+ A$ toxin-antitoxin $+ Z$ epitoxoid antitoxin. By toxoids are designated both protoxoids and syntoxoids.

To find epitoxoids, his first step is to add as much toxin toxoid mixture to the quantity of the toxic fluid which just neutralized one unit of antitoxin, as shown by the complete health after its injection of the guinea-pig, as will suffice to produce death on the fourth day. This amount will always be found to be above three fatal doses. This apparently excessive amount he believes to be explained by the fact that part of the almost harmless epitoxoids has been displaced by toxin. Ehrlich considers death on the fourth day to be caused by one free minimal fatal dose of toxin.

Let us, as Ehrlich, lump syntoxoids and protoxoids together under the name "toxoids," then suppose we have a toxin composed of 50 toxin molecules + 50 (syntoxoids and protoxoids) toxoids and 100 epitoxoids. To satisfy these 200 molecules of toxin, toxoids, and epitoxoids we add one unit of antitoxin. After chemical combination we have 50 toxin-antitoxin and 50 toxoid-antitoxin and 100 epitoxoid-antitoxin. To displace the epitoxoids from the antitoxin we would have to add enough fatal doses to contain 100 molecules of toxin and toxoids, this would be then 50 of toxin and 50 of toxoid. A half molecule more of each would leave a pure toxin molecule, which would, according to Ehrlich, cause the guinea-pig's death in four days.

Ehrlich's formula to find the epitoxoids is:

$$\text{Epitoxoids} = \frac{200 \quad (L_{+} - L_0 - 1)^{*}}{L_0 + (L_{+} - L_0 - 1)} \text{ which with the above toxin } = \frac{200 \times 50}{50 + 50} = 100.$$

The above summary merely gives an outline of Ehrlich's most interesting article. To become fully acquainted with the reasons for his theories the article itself must be carefully read. He concludes with the statement that his investigations have cleared up the difficulties surrounding the estimation of the amount of antitoxin in any given quantity of serum, and that the formula resulting from his investigations enables us to determine in any selected toxic diphtheria culture fluid the amounts of toxin and toxoid present, so that a unit of antitoxin is no longer a varying quantity, but of an exact and determinable size and one which can at any time be reproduced.

Interest in both his theoretical reasoning and in his practical conclusions led us to subject both to a series of tests which have, I believe, added some interesting facts to those already published by Ehrlich as well as cast doubts on some of his conclusions.

The results of these experiments of Park and Atkinson (*Journal of Experimental Medicine*, Vol. III., No. 4) were fully in accord with those published by Ehrlich, as to the varying neutralizing value of a minimal fatal dose of "toxin"; they, however, also indicate roughly a general law in accordance with which these changes occur.

The neutralizing value of a fatal dose of toxin is at its lowest in the culture fluid when the first considerable amounts of toxin have been produced. After a short period, during which the quantity of toxin in the fluid is increasing, the neutralizing value of the fatal dose begins to increase, at first rapidly, then more slowly.

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* 200 = number of molecules of toxin or toxoid required according to Ehrlich to neutralize one unit of antitoxin.

$L+$ = fatal doses of toxin required to kill a guinea-pig in four days after having been mixed with one unit of antitoxin.

L_0 = fatal doses of toxin required to fully neutralize one unit of antitoxin.

1, though given by Ehrlich, appears to me to be incorrect, for by his own statement one molecule of toxin and toxoid should be added, not 1 of toxin (1 fatal dose) alone. The amount to be substracted from the difference between $L+$ and L_0 would therefore be, not 1, but a fraction of 1.

While the culture is still in vigorous growth and new toxin is being produced, the neutralizing value of the fatal dose fluctuates somewhat, but with a generally upward tendency. After the cessation of toxin production the neutralizing value of the fatal dose increases steadily until it becomes five to ten times its original amount.

In our experiments the greatest value for L+ was 126, the least 27. As at 6 hours L+ was only 72 and at 28 hours only 91, we doubt whether L+ ever reaches above 150, and therefore hardly expect Ehrlich's figures of 200 to be realized. When we seek to analyze the above-described process, we find certain facts which seem partly to explain it. Experiments have shown that filtered toxin, preserved for any length of time in conditions under which access of air occurs, gradually loses in both its toxicity and neutralizing power, and that it loses more rapidly in the former property than in the later. Thus, while the fatal dose of a toxin preserved for one year rose from .01 c.c. to .55 c.c., it lost only half as much in neutralizing value, one unit neutralizing at first 1 c.c., at the end of the year .25 c.c. These processes take place more rapidly at room temperature than in the ice chest, and in the incubator than in the room.

In the fluid holding the living bacilli we have, therefore, after the first few hours of toxin formation, a double process going on, one of deterioration in the toxin already accumulated, which tends to increase the neutralizing value of the fatal dose, the other of new toxin formation, which probably tends to diminish the neutralizing value. The chemical changes produced by the growth of the bacilli in the bouillon tend to aid one or the other of these processes and so to make from hour to hour slight changes in the value of the fatal dose. Later, with the period of cessation of toxin production, the gradual deterioration of the toxicity alone continues, and the fatal dose gradually and steadily increases in its neutralizing value.

Ehrlich's theories, as to the splitting up of "toxin" into toxoids having little or no toxicity but on the average full neutralizing power for antitoxin, have not in our opinion been substantiated by the results of these experiments. The difference between the amount of toxin mixed with a unit of antitoxin which causes the first symptoms and that causing death upon the fourth day would be, it is true, explained by his theory; but the failure of this difference to be greater where, by his theories, epitoxoids should be in great abundance prevents our acceptance of his views. The fact of the greater neutralization value of a fatal dose of a deteriorated toxin would be accounted for on his protoxoid theory. This, however, is not proof of its correctness, as other theories, such as the production by the diphtheria bacillus of two or more closely allied toxins, similar to the allied alkaloids produced by plants, would equally account for it, if we supposed the one which had the greater neutralization value was more resistant to destruction than the other. We only advance this theory to call attention to the fact that many theories can on paper explain a process without necessarily being thereby established.

Even if his theories prove partially correct, we feel certain that his formula for standardizing toxins is founded upon error and cannot be employed for the puropse intended by him.

While we do not believe, therefore, that he has changed the principles of testing antitoxin, yet we believe he has contributed greatly to uniformity in results by calling attention to the necessity of selecting a suitable toxin and by employing and distributing an antitoxin as a standard to test toxins by. In this way smaller testing stations can make their results correspond with those of the central station.

In spite of the great variations in the neutralizing value of a fatal dose in different toxins, we do not believe there has been any such great difference in the toxins used by the different stations for testing purposes. Most laboratories have taken the culture fluid at about the time of its greatest toxicity, and the neutralizing value of a fatal dose of this toxin would seldom vary more than ten per cent. above or below the standard now adopted in Germany by the government testing station, this latter being presumably as close as possible to that used to establish the original Behring-Ehrlich unit.

Where error has been made, it has usually been by taking too old culture fluids, which would cause the antitoxin strength of samples tested to be estimated below and not above its real value. Culture 8, which is used not only by the New York Board of Health laboratory but by many other laboratories in the United States and Europe, fortunately produces on the sixth day, the time at which the culture is usually removed, a toxin which grades Ehrlich's antitoxin within five per cent. of the strength given by him.

We believe that by using such a bacillus, we can, after gaining a fuller knowledge of its characteristics, obtain a toxin of a known and suitable neutralizing value, and thus always correctly standardize an antitoxic serum. This is certainly true for the bacillus which we have used for the past three years. Meanwhile a fairly permanent antitoxin, such as Ehrlich provides, is of immense value in insuring a uniform though not necessarily correct standard among the different testing stations and in allowing of comparison between them.

The old definition of Behring and Ehrlich, that an antitoxin unit has the amount of antitoxin which protected the life of a guinea-pig from one hundred fatal doses of toxin, must be modified so as to be defined as that amount of antitoxin which will neutralize one hundred fatal doses of a toxin similar to that adopted as the standard, namely, one having the characteristics of toxins in cultures at the height of their toxicity.

PATHOLOGICAL ANATOMY.

The lesions in uncomplicated diphtheria are due to the effect of the specific toxin formed by the diphtheria bacillus which is absorbed by the tissues in contact with the exudate, and from them diffuses throughout the body. In the cases complicated by pneumonia, general septicæmia, etc., the lesions due to the pyogenic cocci or other organisms are added.

The most characteristic feature of diphtheria is the formation of an exudate or pseudomembrane. This usually appears on the mucous membrane of the tonsils, uvula, soft palate, pharynx, and nose. It frequently, however, attacks the larynx, trachea, and even the bronchi, either primarily or as an extension from the pharynx. Upon the mucous membrane of the tonsils and adjacent organs the lesions usually first appear as white thin patches of exudate or pseudomembrane. Later in severe cases the membrane becomes thick, covering a large portion of the mucous membrane, and may have a dirty gray or yellowish tinge.

The tissues underlying and surrounding the pseudomembrane are more or less intensely hyperæmic and swollen. When the membrane is thick and adherent, it leaves on being torn off a bleeding surface which is quickly covered anew by false membrane. In some of the milder cases the exudate may easily be rubbed off and no bleeding occurs.

The membrane may be made of visible layers, and they may be peeled off one from another. This is especially true of that covering the uvula and soft palate, both of which may be œdematous and enormously swollen. The membrane in the larynx and trachea is of less thickness, and usually is less tough than that of the pharynx and soft palate.

Although, as a rule, the exudate in the larynx is thin and friable, yet at other times it is thick and fibrous, so that a complete cast of the larynx and trachea may be coughed up or torn off. The swelling of the submucous connective tissue in the region of the ventricles of Morgagni, the false cords, and the aryepiglottic folds may give rise to marked obstruction to the breathing space.

The formation of the pseudomembrane is due to the action of the toxin, and is composed of the necrosed epithelium, of bacteria, and of coagulable serous exudate. This exudate is thrown out gradually, and thus may be formed in several layers.

The connective tissue of the mucous membrane is hyperæmic and infiltrated. Sooner or later the epithelium under the pseudomembrane is partly or completely lost, and the underlying tissue is covered instead with a network of fibrin which contains more or less partly or completely degenerated epithelial cells and leucocytes.

This network of fibrin frequently extends down into the submucous tissues. The fibrinous mass may be composed of a very fine reticulum of fibrin or of a narrow-meshed network of tolerably thick bands. It may either contain many leucocytes in the spaces of the network or be mostly devoid of cellular elements. The superficial layer of the false membrane is frequently found early in the disease already broken down into granular detritus and permeated by masses of cocci and diphtheria bacilli. The degenerated epithelium usually disappears entirely by solution or desquamation, but isolated vestiges may still be met with beneath the membrane when the epithelium has not become necrotic in its whole thickness, and also when the exudation has spread over adjoining portions of mucous membrane where the epithelium has not degenerated. The tissues beneath the pseudomembrane are always more or less the seat of small-celled infiltration, and frequently also of fibrinous exudate or hemorrhage. The blood-vessels are congested, the lymph channels dilated and filled with fluid rich in fibrin.

If the necrosis in diphtheria restricts itself to the epithelium, healing will take place without the formation of a scar.

The necrosis may, however, extend to the connective tissue, in which case the tissue of the latter, including the vessels, may be entirely destroyed. There may be also in the tonsils and adenoid tissues areas of necrosis. In these cases a depression is left which fills up with granulation or cicatricial tissue.

Heart.—The pathological changes in the heart are among the most important lesions in severe diphtheria. The heart wall in the severe cases is flabby, and both ventricles are usually dilated, or only the right. Marked parenchymatous degeneration of the heart fibres up to almost complete fatty metamorphosis may occur. The muscle fibres are degenerated, the nuclei are broken down or have disappeared, and the fibres themselves cease to be continuous. The endothelium of the vessels is swollen and the leucocytes are increased, and hemorrhages may be present between the muscle fibres. These alterations are only marked in the late cases; in those quickest fatal only slight parenchymatous changes are apparent. The valves of the heart may be the seat of fibrinous deposits. In the pericardium there may be collections of serous or more rarely purulent fluid.

Kidneys.—In most severe cases the kidneys are in a state of more or less acute nephritis. The kidneys are usually hyperæmic and enlarged, more rarely anæmic. The capsule is commonly non-adherent; the surface of the kidney is smooth, and is frequently the seat of small hemorrhages. Upon the cut surface the markings are indistinct and show degenerative parenchymatous changes. The cortex is thickened and reddish-gray or yellowish-gray in color. Microscopically, the signs of marked parenchymatous changes are evident up to complete necrosis of the epithelium lining the tubules. In these tubules evidences of hemorrhages and casts are found. The epithelium of the glomerular capsules is swollen and proliferated, and the vessels of the tufts are compressed by hemorrhages and exudates into the capsule. The endothelium in the walls of the kidney vessels is found proliferated or undergoing degeneration. Frequent and small hemorrhages occur through the walls of the vessels. In severe cases the urine as a rule contains abundant albumin, degenerated kidney epithelium, leucocytes, and hyaline casts, and in the most severe coarse and fine granular casts. Blood cells are infrequent.

The adenoid tissue of the spleen, intestines, and lymphatic glands shows the same areas of increased leucocytes and the same necrosis and hyaline degeneration of the tissue cells as are found in the kidneys and other organs.

The submaxillary *lymph glands* are enlarged, often hemorrhagic, and may even be the seat of suppuration. The lungs in cases of laryngeal diphtheria are frequently the seat of more or less extensive areas of bronchopneumonia or of general bronchitis. These lesions are due more to the pneumococcus and streptococcus infection than to the diphtheria bacillus. Subpleural ecchymosis is frequent, and the lungs exhibit areas of atelectasis or emphysema. The changes in the lungs become in a considerable number cf laryngeal cases of more serious importance than the earlier diphtheritic lesions.

Nervous System.—The lesions produced by the diphtheria toxin upon the nerve tissues are of the greatest importance and are well summed up by J. J. Thomas after a recent investigation reported in the *Boston Medical Journal* of February 10th, 1898. (1) A marked parenchymatous degeneration of the peripheral nerves, sometimes accompanied by an interstitial process, and hyperæmia and hemorrhages; (2) acute diffuse parenchymatous degenerations of the nerve fibres of the cord and brain; (3) no changes but slight ones in the nerve cells; (4) acute parenchymatous and interstitial degeneration in the muscles, especially the heart muscle; (5) occasional hyperæmia, or infiltration, or hemorrhage in the brain or cord, in rare cases severe enough to produce permanent troubles, such as the cases of multiple sclerosis and of hemiplegia which have been observed.

Finally the probability that the cases of sudden death from heart failure in diphtheria during the disease or convalescence are due to the effect of toxic substances produced in the disease upon the nerve structures of the heart. To these changes in the peripheral nerves are due the paralysis of the muscles of the palate, pharynx, heart, and voluntary muscles. In convalescent cases the nerve lesions disappear usually in the course of several weeks or months, to an extent sufficient to allow the nerves to renew their functions.

Blood Changes.—The changes in the blood are caused not only by the absorbed toxins from the diphtheria bacilli and associated micro-organisms situated at the seat of the diphtheritic inflammation, but also frequently in the laryngeal cases by the action of streptococci or other cocci circulating in the blood itself, for in many of these cases a true septicæmia develops. Diphtheria is usually attended by pronounced leucocytosis. The increase of leucocytes begins a few hours after the infection, probably appearing earlier in refractory individuals, and often being long delayed in susceptible cases with severe infection. In a careful investigation of the leucocytosis in diphtheria, Ewing (*New York Medical Journal*, August 10th, 1895) found that in favorable cases the leucocytosis is greatest at the climax of the disease, and steadily declines during convalescence. There may, however, be prolonged hyperleucocytosis after other local and constitutional symptoms have subsided.

In unfavorable cases the leucocytosis continues until death; but in somewhat prolonged cases, with much septic absorption, there may be an uninterrupted decrease of leucocytes continuing up to the fatal termination.

A complicating pneumonia usually causes a considerable increase in leucocytosis.

The degree of leucocytosis in diphtheria often varies with the fever, but much more frequently corresponds to the extent of the local lesions.

The intravascular leucocytosis of diphtheria appears to measure the systemic reaction against the toxic products circulating in the blood and absorbed from the site of infection.

A high degree of leucocytosis in diphtheria indicates a pronounced reaction against a severe infection, but it is not necessarily an unfavorable prognostic sign.

Steadily decreasing leucocytosis usually, but not always, accompanies a favorable course in the disease.

Slight leucocytosis usually indicates a mild infection, but fatal cases may for several days show no increase, or maybe even a decrease, in the number of leucocytes.

The staining reaction of the leucocytes appears to be an accurate measure of the severity of a diphtheritic infection, and variations in this reaction often precede changes in other symptoms.

Antitoxin within thirty minutes after its injection causes a hypoleucocytosis, the reduction affecting specially the uninuclear leucocytes, while the proportion of well-stained multinuclear cells is increased. This action is due largely to the immunizing principle contained in the serum.

The red blood cells are also profoundly influenced in the more severe cases of diphtheria. There is marked diminution in the number of the red cells and frequently also in their percentage of hæmoglobin. This anæmia persists in some cases for considerable periods after recovery from the local inflammation. In this connection it is of interest that horse serum which is given with diphtheria antitoxin also causes in some cases a considerable diminution in the number of red blood cells. By neutralizing the still more deleterious diphtheria toxin the total effect of the antitoxic horse serum is to lessen the anæmia which would occur from untreated diphtheria. In a certain number of the very grave cases minute or larger hemorrhages occur in the skin, mucous and serous membranes, and retinæ. These hemorrhagic extravasations are probably due to changes in both the blood-vessels and blood.

DIAGNOSIS.

In deciding whether a doubtful case is one of diphtheria or not, it is necessary to take into account whether the patient has been exposed to diphtheria, to scarlet fever, or to other infectious diseases.

If in any case exposure to diphtheria is known to have occurred, even a slightly suspicious sore throat must be regarded as probably a mild diphtheria. If, on the other hand, no cases of diphtheria have been known to exist in the neighborhood, even cases of a more suspicious nature would probably not be diphtheria.

In judging from the appearance and symptoms of a case one must first acknowledge that there are certain mild exudative inflammations of the throat belonging both to diphtheria and pseudodiphtheria which appear exactly alike, have apparently similar symptoms and similar duration. It is even possible to examine two cases, knowing that one is surely diphtheria, or at least that diphtheria bacilli are present in the exudate, and the other surely is not, and yet be unable to determine clinically which is true diphtheria and which is pseudodiphtheria. It is not meant to imply that a case is one of true diphtheria simply because the diphtheria bacilli are present, but rather that the doubtful cases not only have the diphtheria bacilli in the exudate, but are capable of giving true characteristic diphtheria to others, or later develop it themselves; and that those in whose throats no diphtheria bacilli exist can under no condition give true characteristic diphtheria to others or develop it themselves unless they receive a new infection. It is indeed true, as a rule, that cases presenting the appearance of ordinary follicular tonsillitis in adults are not diphtheria. It is also true that now and then a case having this appearance is one of diphtheria, and almost every physician has seen such cases from time to time in households infected with diphtheria. On the other hand, in small children mild diphtheria very frequently occurs with the semblance of rather severe ordinary follicular tonsillitis, and in large cities where diphtheria is prevalent all such cases must be watched as more or less suspicious.

Appearances Characteristic of Diphtheria.—The presence of irregular-shaped patches of adherent grayish or yellowish-gray pseudomembrane on some other portions than the tonsils, is, as a rule, diagnostic of diphtheria. Restricted to the tonsils alone the diagnosis is less certain.

Occasionally in scarlatinal angina or in severe phlegmonous sore throats patches of exudate may appear on the uvula or borders of the faucial pillars, and still the case may not be one of true diphtheria; these are, however, exceptional. Thick grayish pseudomembranes which cover large portions of the tonsils, soft palate, and nostrils are almost invariably the lesions of true diphtheria.

The very great majority of cases of pseudomembranous or exudative laryngitis, whether an exudate is present in the pharynx or not, are cases of true diphtheria. Cases in which no exudate is apparent and those in which the laryngeal obstruction is sudden and the spasmodic element is marked, are frequently non-diphtheritic catarrhal laryngitis; but the absolute exclusion of diphtheria is never safe, and, as a rule, antitoxin should be given before waiting for the further course of the disease or the results of the bacteriological examination to clear up the diagnosis. Nearly all cases in which membrane is present in the nose are true diphtheria. When the membrane is limited to the nose the symptoms are, as a rule, very slight, but when the nasopharynx is involved the symptoms are usually grave. Usually a small area of inflammation indicates a slight or moderate severity and an extensive area a severe infection.

Most cases of pseudomembranes and exudates entirely confined to portions of the tonsil or tonsils in adults are not diphtheria, although a few cases presenting these symptoms are. The more complete the involvement of the tonsils the more apt the case is to be diphtheria.

Cases presenting the appearances found in scarlet fever, in which a thin grayish membrane lines the borders of the uvula and faucial pillars, are rarely diphtheritic. As a rule, pseudomembranous inflammations complicating scarlet fever, syphilis, and other infectious diseases are not diphtheria. But from time to time such cases, if they have been exposed to diphtheria, may be complicated by it, and in some epidemics mixed infection is common.

The Exudate in Diphtheria Contrasted with that in Pseudodiphtheria.—As a rule, the exudate in diphtheria is firmly incorporated with the underlying mucous membrane, and cannot be removed without leaving a bleeding surface, at least until convalescence. The tissues surrounding the exudate are more or less inflamed and swollen. In pseudodiphtheria the exudate is usually loosely attached, collected in small masses, and easily removable. Exceptions, however, occur in both these diseases, so that in true diphtheria the exudate may be easily removed and in pseudodiphtheria the exudate may be firmly adherent. It is therefore impossible to make the diagnosis certain from the adherence of the exudate to the mucous membrane.

In the absence of scarlet fever the occurrence of albuminuria with casts will enable a probable diagnosis of diphtheria to be made. This may aid both in a case in which the membrane is removed from observation and in one already convalescent. Some pseudomembranous inflammations which are not diphtheria give rise to nephritis and albuminuria.

Paralysis following a pseudomembranous inflammation is an almost positive indication that the case was one of diphtheria, although slight paralysis has followed in a very few cases in which careful cultures revealed no diphtheria bacilli. These, if not true diphtheria, must be considered very exceptional cases.

Bacteriological Diagnosis.

From the above it is apparent that fully developed characteristic cases of diphtheria are readily diagnosticated, but that many of the less marked or at an early period undeveloped cases are difficult to differentiate the one from the other. In these cases cultures are of the utmost value, since they enable us to isolate those in which the bacilli are found, and to give preventive inoculations of antitoxin, to both the sick and those in contact with them. As a rule, cultures do not give us as much information as to the gravity of the case as the clinical appearances, for by the end of twenty-four to forty-eight hours the extent of the disease is usually easy of determination. The absence of bacilli in a culture must be given weight in proportion to the skill with which the culture was made and with which it was examined.

TECHNIQUE OF THE BACTERIOLOGICAL DIAGNOSIS.

Collection of the Blood Serum and its Preparation for Use in Cultures.—A covered glass jar, which has been thoroughly cleansed with hot water, is taken to the slaughter-house and filled with freshly shed blood from a calf or sheep. The blood is received directly in the jar as it spurts from the cut in the throat of the animal. After the edge of the jar has been wiped, it is covered with the lid and set aside where it may stand quietly until the blood has thoroughly clotted. The jar is then carried to the laboratory and placed in an ice chest. If the jar containing the blood is carried about before the latter has clotted, very imperfect separation of the serum will take place. It is well to inspect the blood in the jar after it has been standing a few hours, and if the clot is found adhering to the sides, to separate it by a rod. The blood is allowed to remain twenty-four hours on the ice, and then the serum which surrounds the clot is siphoned off by a rubber tube and mixed with one-third its quantity of nutrient beef broth, to which one per cent. glucose has been added. This constitutes the Loeffler blood-serum mixture. The broth used to mix with the serum is prepared as follows: One pound of finely chopped lean beef is allowed to soak in one litre of water in a cool place for at least twelve hours. The meat and fluid are now dumped into a cheese-cloth or towel and as much as possible of the fluid portion is squeezed out. To this solution one per cent. of peptone, one per cent. of glucose, and one-half per cent. of common salt are added. It is well to test the reaction of the mixture, and if it is found to be acid, to render it neutral by adding a few drops of a solution of caustic soda or carbonate of sodium. The whole is now boiled for half an hour, and filtered through absorbent cotton or filter paper. If the broth is to be kept, it should be placed in flasks and sterilized. The Loeffler blood-serum mixture when ready is poured into tubes, which should be about four inches in length and two-thirds of an inch in diameter. These tubes should first be plugged with cotton and sterilized by dry heat at 150° C. for one hour. Care should be taken in filling the tubes to avoid the formation of air bubbles, as they leave a permanently uneven surface when the serum has been coagulated by heat. To prevent this, the end of the pipette or funnel which contains the serum should be inserted well into the test tube. About 2 c.c. are sufficient for each tube. The tubes, having been filled, are now to be coagulated and sterilized. They are placed at the proper angle, and then kept for two hours at a temperature just below the boiling point. For this purpose a Koch serum coagulator or a double boiler serves best, though a steam sterilizer will suffice. If the latter is used, a wire frame must be arranged to hold the tubes at the proper inclination, and the degree of heat must be carefully watched, as otherwise the temperature may go too high, and if the serum is actually boiled, the culture medium will be spoiled. After sterilization by this process, the tubes containing the sterile, solidified blood serum can be placed in covered tin boxes and kept for months. The serum thus prepared is quite opaque and firm. A mixture of blood cells renders the serum darker, but it is not less useful.

The Swab for Inoculating Culture Tubes.—The swab to inoculate the serum is made as follows: A stiff, thin iron rod, six inches in length, is roughened at one end by a few blows of a hammer, and about this end a little absorbent cotton is firmly wound. Each swab is then placed in a separate glass tube, and the mouths of the tubes are plugged with cotton. The tubes and rods are then sterilized by dry heat at about 150° C. for one hour, and stored for future use. These cotton swabs have proved much more serviceable for making inoculations than platinum wire needles, especially in young children and in laryngeal cases. It is easier to use the cotton swab in such cases, and it gathers up so much more material for the inoculation that it has seemed more reliable.

For convenience and safety in transportation a "culture outfit" has been devised (Fig. 5), which consists of a small wooden box containing a tube of blood serum, a tube holding a swab, and a record blank. These "culture outfits" may be carried or sent by messenger or express to any place desired, and in New York are kept at stations scattered throughout the city for the free use of physicians.

Directions for Inoculating Culture Tubes with the Exudate.—The patient is placed in a good light, and, if a child, properly held. The swab is removed from its tube and, while the tongue is depressed with a spoon, is passed into the pharynx (if possible, without touching the tongue or other parts of the mouth) and is rubbed gently but firmly against any visible membrane on the tonsils or in the pharynx, and then, without being laid down, the swab is immediately inserted in the blood-serum tube, and the portion which has previously been in contact with the exudate is rubbed a number of times back and forth over the whole surface of the serum. This should be done thoroughly, but it is to be gently done, so as not to break the surface of the serum. The swab should then be replaced in its tube, and both tubes, thin cotton plugs having been inserted, are reserved for examination, or sent to the laboratory or collecting station (as in New York City). If sent to the health-department laboratories for examination, the blank forms of report which usually accompany each "outfit" should be filled out and forwarded with the tubes.

Where there is no visible membrane (it may be present in the nose or larynx) the swab should be thoroughly rubbed over the mucous membrane of the pharynx and tonsils, and in the nasal cavities, and a culture made from these. In very young children care should be taken not to use the swab when the throat contains food or vomited matter, as then the bacteriological examination is rendered more difficult. Under no conditions should any attempt be made to collect the material shortly after the application of disinfectants (especially solutions of corrosive sublimate) to the throat.

Examination of Cultures.—The culture tubes which have been inoculated, as described above, are kept in an incubator at 37° C. for twelve hours, and are then ready for examination. When great haste is required, even five hours will often suffice for a sufficient growth of bacteria for a skilful examiner to decide as to the presence or absence of the bacilli. On inspection, it will be seen that the surface of the blood serum is dotted with numerous colonies, which are just visible. No diagnosis can be made from simple inspection; if, however, the serum is found to be liquefied or shows other evidences of contamination, the examination will probably be unsatisfactory.

A microscopical preparation is now made by placing a small drop of water upon a clean cover-glass, and then a platinum needle is inserted in the tube, and quite a large number of colonies are swept with it from the surface of the culture medium. The bacteria adherent to the needle are washed off in the drop of water previously placed on the cover-glass and smeared over its surface. The bacteria on the glass are then allowed to dry in the air. The cover-glass is then passed quickly through the flame of a Bunsen burner or alcohol lamp, three times in the usual way, covered with a few drops of Loeffler's solution of alkaline methylene blue, and left without heating for ten minutes. It is then rinsed off in clear water, dried, and mounted in balsam.

In the great majority of cases one of two pictures will be seen with the one-twelfth oil-immersion lens: either an enormous number of characteristic Loeffler bacilli with a moderate number of cocci, or a pure culture of cocci, mostly in pairs or short chains (see Figs. 6 and 10). In a few cases there will be an approximately even mixture of Loeffler bacilli and cocci, and in others a great excess of cocci. Besides these, there will be occasionally met preparations in which, with the cocci, there are mingled bacilli more or less resembling the Loeffler bacilli. . These bacilli, which are usually of the pseudodiphtheria type of bacilli (see Figs. 8 and 9), are especially frequent in cultures from the nose.

In not more than one case in twenty will there be any serious difficulty in making the diagnosis, if the serum tube has been properly inoculated. In such a case another culture must be made or the bacilli plated out and tested in pure culture.

Direct Microscopical Examination of the Exudate.—An immediate diagnosis, without the use of cultures, is often possible from a microscopical examination of the exudate. This is made by smearing a cover-glass with a little exudate from the swab, drying, staining, and examining it microscopically. This examination, however, is much more difficult, and the results are more uncertain than when the covers are prepared from cultures. The bacilli from the membrane are usually less typical in appearance than those found in cultures, and they are mixed with fibrin, pus, and epithelial cells. They may also be very few in number in the parts reached by the swab, or bacilli may be met with which closely resemble the Loeffler bacilli in appearance, but which differ greatly in growth and in other characteristics. When in a smear containing mostly cocci a few of these doubtful bacilli are present, it is impossible either to exclude or to make the diagnosis of diphtheria with certainty. Although in some cases this immediate examination may be of the greatest value, it is not a method suitable for general use.

Occasionally a culture of only six hours' growth in the incubator will have developed sufficiently to show characteristic diphtheria bacilli when stained and examined microscopically, though as a rule the bacilli do not stain so well as in the older cultures. In urgent cases, however, in which time is a matter of importance, this method is often of great value.

Animal Inoculation as a Test of Virulence.—If the determination of the virulence of the bacilli found is of importance, animal inoculations must be made. Experiments on animals form the only method of determining with certainty the virulence of the diphtheria bacillus. For this purpose, alkaline broth cultures of forty-eight hours' growth should be used for the subcutaneous inoculation of guinea-pigs. The amount injected may vary from one-fourth to one-half per cent. of the body weight of the animal inoculated. In the large majority of cases, when the bacilli are virulent, this amount causes death within seventy-two hours. At the autopsy the characteristic lesions already described are found. Bacilli which in cultures and in animal experiments have shown themselves to be characteristic may be regarded as certainly true diphtheria bacilli, and as capable of producing diphtheria in man under favorable conditions.

For an absolute test of specific virulence antitoxin may be used. A guinea-pig is injected with antitoxin, and then this and a control animal with a multiple of the fatal dose of a broth culture of the bacilli to be tested; if the guinea-pig which received the antitoxin lives while the control dies, it was surely a diphtheria bacillus which killed by means of diphtheria toxin—or, in other words, not simply a virulent bacillus but a virulent diphtheria bacillus.

The practical conclusions to be derived from investigations into the bacteriological diagnosis of diphtheria may be summarized as follows:

1. All inflammation of the mucous membrane due to the diphtheria bacillus of Loeffler should be included under the name "diphtheria." An acute hyperæmia of the mucous membrane caused by the Loeffler bacilli is considered as truly diphtheria in the sense of its infectiousness as an inflammation with pseudomembrane or exudate, and a case in which the lesions are confined to the larynx or bronchi as truly diphtheria as one in which the tonsils and pharynx are involved. In well-developed cases the extent and location of the disease are of perhaps even greater importance than the bacterial cause in judging of the gravity of the disease.

2. Under pseudodiphtheria or some other name than diphtheria should be included all inflammations of the mucous membranes which simulate true diphtheria and which are due to streptococci or, more rarely, other cocci.

3. The name croup or membranous croup should be regarded as a term merely indicating that the location of the pseudomembranous or exudative lesion is in the larynx, and not describing the nature of the disease, whether diphtheritic or pseudodiphtheritic. In New York City at the present time, from eighty to ninety per cent. of the cases of persistent "croup" are diphtheria.

4. The examinations of cultures made upon solidified blood serum under proper conditions form a fairly reliable method of determining whether the diphtheria bacillus is present or absent in a throat. For diagnostic purposes, cultures should be made before the pseudomembrane or exudate begins to disappear.

5. Virulent diphtheria bacilli were apparently present in about one per cent. of the healthy throats in New York City at the time of these investigations and a somewhat similar condition probably exists in other cities. Diphtheria, however, was rather prevalent in the city at that time. Most of the persons in whose throats the bacilli exist have been in direct contact with cases of diphtheria. Very many of those whose throats contain the virulent bacilli never develop diphtheria, while in others after exposure, digestive disturbances, or other predisposing causes the disease occurs. We must therefore conclude that the members of a household in which a case of diphtheria exists should be regarded as sources of danger, unless cultures from their throats show the absence of diphtheria bacilli.

6. The bacilli found in the original serum cultures, which in appearance and staining are identical with the typical Loeffler diphtheria bacillus, may be regarded, for diagnostic purposes, as virulent diphtheria bacilli, if the cultures have been made either from throats containing exudate or from those of persons who have been in contact with true diphtheria, for investigation has shown that over ninety-five per cent. of such bacilli are virulent.

7. All bacilli which are identical with the virulent Loeffler diphtheria bacillus, morphologically, biologically, and in staining by reagents, should be classed with the diphtheria bacilli, whether they have much, little, or no specific virulence when tested in guinea-pigs. Bacilli which have entirely lost their virulence rarely, if ever, regain it. They probably are incapable of causing diphtheria, for so far as is known cases in which they were found never developed any lesions, nor were they the origin of any case of diphtheria.

8. The name pseudodiphtheria bacillus if used at all should be regarded as applying to those bacilli found in the throat which, though resembling the diphtheria bacilli in many respects, yet differ constantly from them. These bacilli are rather short and are more uniform in size and shape than the Loeffler bacillus. They stain, as a rule, equally throughout with the alkaline methyl blue solution, rarely show the polar bodies with the Neisser stain, and produce alkali in their growth in bouillon. They are found in about one per cent. of the healthy throats in New York City, and seem to have no connection with diphtheria. They never produce appreciable diphtheria toxin and are only pathogenic in guinea-pigs when enormous doses are given.

9. One or more varieties, both of streptococci and other forms of pyogenic cocci, exist in the great majority, and possibly in all, of the healthy throats in crowded cities. Cultures from the throats in cases of pseudodiphtheria contain a larger percentage of cocci, especially of streptococci, than those from healthy throats, but otherwise do not seem to differ.

10. Investigations carried out in cities in many parts of Europe and America have given striking evidence of the marked difference in mortality between true and pseudodiphtheria. Thus while in the cases coming under the cognizance of the New York Health Department during a long period of time it was twenty-seven per cent. in diphtheria, it was under two per cent. in pseudodiphtheria.

11. The combined clinical and bacteriological investigation of over five thousand cases has demonstrated clearly the fact that many of the less characteristic cases of diphtheria and pseudodiphtheria are so

similar in appearance, symptoms, and duration that it is impossible to separate them, except by bacteriological examinations. In the more severe cases and after the disease has fully developed, cultures are less necessary, although their systematic use is desirable.

12. Persons who have suffered from diphtheria should be kept at least partially isolated until cultures prove that the bacilli have disappeared from the throat, for not only are the bacilli which persist in the throat virulent, but they are not infrequently the cause of diphtheria in others. When cultures cannot be made, isolation should be continued for at least three weeks after the disappearance of the membrane, for experience has shown that it is not unusual for the bacilli to persist this length of time.

13. In pharyngeal cases in which thorough irrigation of the nostrils and throat has been practised frequently, the bacilli have not remained in the throat for as long a time after the complete disappearance of the pseudomembrane as when no antiseptic or cleansing solution has been employed. Other cleansing and antiseptic solutions are also useful. In some cases the bacilli persist for a number of weeks in spite of the use of antiseptic or cleansing solutions.

14. Inflammations of the mucous membranes due to streptococci, either alone or associated with other cocci, are usually mild in character. These inflammations may be more serious when the lesions are located in the larynx, when they are complicated by scarlet fever or measles, or when the deeper tissues become infected.

15. While the streptococci and perhaps other forms of cocci may be considered as the primary etiological factor in pseudodiphtheria, yet, in the majority of cases at least, certain predisposing conditions, such as exposure to cold or other deleterious influences or the presence of certain infectious diseases, appear to be of great importance in determining the occurrence of the disease.

The streptococci which under these conditions apparently cause the disease are probably those which had for a long time existed in the throat, and not those freshly derived through communication with other cases of pseudodiphtheria. In a small number of cases, indeed, the histories suggest a direct communication; but the causation may be equally well explained by the supposition that the second case shared with the original one the same predisposing cause.

16. The slight mortality and the usual mildness of the cases of pseudodiphtheria do not warrant the enforcing of isolation, even if further investigation produced positive proof that this disease is directly communicable.

17. Diphtheria antitoxin renders inert the specific toxin of the

diphtheria bacillus, and indirectly, by preventing the inflammatory changes in the mucous membranes due to the toxin, limits the growth of the bacillus.

18. Diphtheria antitoxin injected subcutaneously in sufficient amount (300 to 500 units, according to the size of the individual) will protect from an attack of diphtheria for at least two weeks. A repetition of the injection will continue the immunity.

19. Injections of from 1,500 to 6,000 units will exert a curative effect in diphtheria by preventing the continuance of the deleterious effects of the toxin after the absorption of the antitoxin. Tissue injuries already produced are not influenced. Diphtheria antitoxin is a preventive of further injury rather than a curative agent, and should therefore be given early to accomplish the most good.

DIPHTHERIA.

(SYMPTOMATOLOGY AND TREATMENT.)

BY

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NEW YORK.

DIPHTHERIA.

(SYMPTOMATOLOGY AND TREATMENT.)

INTRODUCTION.

Definition.

Diphtheria is a specific, infectious, and contagious disease characterized principally by epithelial changes and by the exudation of fibrin on or in mucous membranes, or on the surface of wounds, or in the denuded rete Malpighi, constituting the so-called pseudomembranes. These are mostly found on the accessible mucous membranes of the digestive and respiratory organs. Their morphological structure in the throat, nares, larynx, and other places is identical, but they have been studied chiefly in the throat, where they are most frequently found. They consist of finely reticulated fibrin holding exudate cells, leucocytes, some few erythrocytes, and characteristic microbes. When they are superficial, it is the epithelial protoplasm which is thus transformed; when they are deep-seated with a tendency to necrosis, ulceration, and finally (if recovery take place) cicatrization, it is the fibrillar basic substance of the connective tissue, chiefly of the mucous membrane, sometimes also of the submucous and deeper structures. This view, which underlies the discussions of all my contributions to the subject of diphtheria since 1860, has lately been again most forcibly demonstrated by Baumgarten (*Berliner klinische Wochenschrift*, Nos. 31 and 32, 1897).

History.

Diphtheria has been epidemic on the Atlantic coast of North America since 1857. The disease was almost unknown at that time—my paper on diphtheria and diphtheritic affections in the *American Medical Times* of August 11th and 18th, 1860, was the first (or among the first?) of those which were written on the subject in our part of the country during the last half century—but the literature has since grown immensely. It was very extensive when I collected it in my essay on "Diphtheria" in the second volume of Gerhardt's "Handbuch der Kinderkrankheiten" (1877). It soon took such dimensions that neither in my "Treatise on Diphtheria" (New York, 1880) nor in Pepper's "American System of Medicine" (Vol. I., 1885), nor in other publications did I do more than refer to authorities for the elucidation of particular points. For many years past it has been the etiology of the disease which has created a literature of its own; so has that part of the subject which treats of antitoxin and of intubation. Symptomatology in all its bearings and morphology have not received many valuable additions; for clinical observations, when correct and correctly reported, are not "subject to change and at the mercy of unknown factors," as a great experimenter has lately said. On the contrary, the vast amount of labor, as exhibited in endless journal articles and books on special topics, which has to be spent on the establishment, verification, or refutation of a single fact in bacteriology, does not prove that "the results obtained by experimentation in the laboratory are unambiguous" to the exclusion of clinical empiricism. Thus it happens that on the following pages I shall frequently repeat statements (many now out of print) which have been found correct in the course of time, and give advice that will still be found serviceable though it was offered decades ago.

Virchow distinguished between croupous and diphtheritic membranes. In his opinion the former was fibrinous with cell proliferations, epithelia, and pus, and was superficial on top of the mucous membrane; the latter was an exudation into the tissue of an amorphous, dense, and coagulated fibrin which did not always injure or implicate the surface epithelium, but would necrose the deeper tissue and give rise to ulceration before healing. But he admitted that complications between the two were very common indeed. Weigert and Cohnheim were of the same opinion as far as the morphological condition and localization of the membranes were concerned; the essential process according to them was a combination of necrosis and inflammation, and their causes, after Recklinghausen and Nassiloff had assumed the primary change to be a microbic invasion, were bacteria and toxins.

According to Wagner the only difference between croup and diphtheria membranes was the fine structure of and the admixture of pus cells to the former. Both of them had their origin in the epithelium, while Buhl looked for it in the mucous membrane itself, in the cells of which nuclear or cystoid proliferations took place.

I cannot detect much difference in the theories which have since been brought forward, for instance, in those of Oertel or of Heubner. The question is always one of degeneration of epithelia, of the presence of leucocytes, an exudation of fibrin, more or less admixture of blood, of hyaline masses, and of new formation of more or fewer round cells in different localities. Oertel comes to the conclusion that, after all, the localization of the process is the final cause of the form and appearance of the pseudomembrane. Why he should make the effort of suggesting the differentiation between a primary and a secondary membrane, the former consisting of direct surface deposits, and the latter of membranous deposits in the tissue which are produced by the presence of other surface deposits in the neighborhood, is not quite intelligible except on the score of "completeness."

For some years it has become customary to distinguish between those pseudomembranes which are caused, or accompanied, by the Klebs-Loeffler bacillus, and those which contain the "pseudobacillus" or staphylococci and principally streptococci. That these microbes do not establish any disease by their mere presence, that on the contrary they are met with to an indefinite degree in the mouths and throats of the healthy, is well understood. That they may be considered pathological, or pathogenic, the presence of pseudomembranes and the presence of the microbes in the pseudomembranes in some stage of development are required. The Klebs-Loeffler bacillus is, however, not always found in every stage of the illness; it appears to perish quite often towards the maceration period. When found it is located in the superficial layers of the pseudomembrane only, and not throughout its whole thickness; the coccus, however, pervades its whole substance, usually in greater numbers in the deeper layers. To explain the absence of Klebs-Loeffler bacilli from these, it is assumed that they are destroyed by other microbes. Still they are credited—in the same way in which they can be proven to do so in the laboratory—with evolving the toxin which gives rise to all the symptoms and dangers of certain forms of constitutional diphtheria.

Pseudomembranes containing Klebs-Loeffler bacilli are called by almost universal agreement *diphtheritic,* those with pseudobacilli and cocci *pseudodiphtheritic.* Local diphtheria ("diphtheritis"), constitutional diphtheritic infection, and diphtheritic sepsis are different degrees of the same disease. The first may run a fairly mild course, or be the initial stage of the second and (or) third. Those cases which present both bacilli and streptococci in their membrane are called cases of *mixed infection.* It has been claimed that cases of the second class, that of streptococcus infection, are of little virulence and attended with but little danger. This opinion leads to cruel mistakes in management, both by boards of health and by such medical men as are influenced by them. For not only are many uncomplicated cases very grave, but the mixed infections are the very worst forms met with in practice. Moreover, the streptococcus cases are contagious, contrary opinions notwithstanding. Still, it is important to mention at once that accurate differentiation has its great practical value, for the reason that it is solely the bacillary variety that can be influenced by the diphtheria antitoxin (see below).

The part played by microbes in diphtheria is not yet absolutely clear. The Klebs-Loeffler diphtheria bacillus and a similar bacillus that is not virulent are found in diabetic and in common tuberculous lungs, in noma, in empyema, on chancres, in ozæna, and in vaccina pustules. It is claimed that there are differences between the two; the pseudodiphtheria bacillus is described as plumper, shorter, and more uniform than the genuine Klebs-Loeffler, but this difference is not so striking as not to be denied by many; nor is there unanimity among different examiners in regard to other differences. Many go so far as to deny the possibility of a differentiation. Loeffler himself has finally come to the conclusion, lately expressed in the Congress of Hygiene at Madrid, that the genuine diphtheria bacillus cannot be diagnosticated in any other way than by its power to generate the diphtheria toxin and by the influence the diphtheria antitoxin has on the bacillus, or rather on the disease. Thus it is acknowledged that there are saprophytes which can be distinguished from genuine diphtheria bacilli by nothing but the absence of virulence.

Another authority, C. Fraenkel, admits that the degree of virulence is so variable that it cannot be employed for differentiation. A very virulent bacillus loses its virulence by a change of the culture medium, and feebly virulent bacilli are rendered highly so by adding streptococci (Roux and Yersin). Moreover Trumpp mixed "pseudobacilli" found in the pus of empyema with diphtheria toxin (not bacilli), made new cultures, and obtained very virulent bacilli; and he found that repeated injections of pseudobacilli would finally kill like genuine bacilli.

F. Schanz (*Deutsche medicinische Wochenschrift*, No. 37, 1898) who lately elaborated these considerations and facts, adds the pertinent remark that a bacillus which is so frequently found on the mucous membranes of the healthy or of the convalescent without the presence of diphtheria, appears to play only an inferior and secondary part in the development of disease. He thinks that the bacillus increases on inflamed surfaces and attains the power of producing a toxin in the membranous exudation only; that it is this toxin which adds to the danger of the disease, and that the presence of streptococci increases its peril; and that it is not impossible at all to assume that diphtheria originates from an unknown cause of its own, but becomes more virulent by the action of the toxin of the Klebs-Loeffler bacillus (with or without the aid of streptococci), whose effect may be destroyed by the diphtheria antitoxin.

Evidently the question of the origin (single or multiple) of diphtheria does not seem to be settled to the satisfaction of all. According to Theobald Smith (*Boston Medical and Surgical Journal*, August 25th, 1898) "it is only clinicians whose voices are sometimes raised against the Klebs-Loeffler bacillus as the chief cause of diphtheria"; but Loeffler himself, and C. Fraenkel, and others equally conscientious, are more careful than formerly in expressing positive views and are less averse to retracing their steps.

There are other questions in connection with diphtheria which seem to be positively settled, for instance, that of the morphology of the pseudomembranes. In Gerhardt's "Handbuch" and in my "Treatise" I studied the subject with a view to elucidate the differences in the condition of morphologically identical pseudomembranes when found in different locations.*

Morphology of Pseudomembranes.

Twenty-five years ago, Trendelenburg infected the trachea of a rabbit with diphtheritic deposits which he had removed from the pharynx and tonsils, in the tissues of which they were deeply and firmly imbedded. The new deposits, however, did not take so deep and firm a hold on the tissues as the original ones, but adhered lightly to the mucous membrane of the trachea to which they had been transplanted. This and many other similar facts cannot be explained by the nature of the pseudomembrane, but by the histological character of the mucous membrane only, which varies with the locality. Its different elements, viz., the epithelium, basement membrane, connective tissue interwoven with elastic fibres, with blood vessels, with nerves from the cerebrospinal and sympathetic systems, and frequently with spindle cells, and the papillæ and ducts of numberless glands, all influence the pathological process going on upon the surface.

The mucous membrane of the *mouth* contains a large number of elastic fibres mixed with cellular tissue and covered by a thick coat of pavement epithelium; its uppermost layer contains flat cells, the second a larger quantity of polygonal cells, and the lowest oval ones which assume a perpendicular relation to the mucous membrane.

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* These bacteriological statements and the following referring to the morphology of pseudomembranes are considered by the author necessary for the explanation of much that he has to say on symptomatology and treatment. They are therefore offered as introductory to the present article without prejudice to the author of the article on the general pathology of diphtheria.

From the mucous membrane a number of papillæ extend into the epithelium, and in this respect they resemble the papillæ of the skin. Acinous muciparous glands are frequent, and most numerous in the anterior aspect of the soft palate. Lymph vessels are very numerous in the lips, tongue, uvula, soft palate, anterior and posterior pillars of the soft palate, and cheeks. The *uvula* contains so many that, if they be injected its circumference is increased two or three fold. They empty into the deep facial lymph bodies to which they communicate diphtheria as well as other infections. The lymphatics of the *tongue* are in intimate connection with the upper layer of the deep cervical, those of the *floor of the mouth* and many from the tongue connect with the submaxillary lymph bodies. The efferent vessels empty their contents into the superior jugular lymph nodes, situated in the trigonum cervicale superius, and finally into the fifteen or twenty inferior jugular (or supraclavicular) nodes which with numerous anastomoses form the jugular lymphatic plexus. The *tonsils* are conglomerations of an indefinite number of follicular bodies, each of which has a thick capsule which is of irregular shape, and consists of connective tissue lined by mucous membrane and pavement epithelium. The connective tissue contains a number of closed follicles, each inclosing numerous lymph corpuscles. The follicles have been considered identical with, or analogous to, the lymph bodies; this assumption is purely problematical, since it has not been possible thus far to verify the existence of afferent or efferent ducts. The practical deduction from this is that the tonsils have little connection with the lymphatic system, and that a disease limited to a tonsil is not liable to infect the organism immediately and intensely.

The mucous membrane of the *nasal cavities* is of varying degrees of thickness; it consists of connective-tissue fibres with numerous nuclei, is free from elastic fibres, but is supplied with a large number of nerves and an abundance of blood-vessels; the Schneiderian membrane possesses in fact a larger number of blood-vessels than do most of the other mucous membranes. That is why, with its submucous tissue, it frequently is the seat of swellings and hemorrhages, as well in diseases of distant organs which give rise to venous stagnation as from the slightest local provocation. The inner surface of the cartilaginous portion is lined with pavement epithelium; the lower region of the real nasal cavities, the so-called respiratory portion, through its whole length supplied with branches of the trifacial nerve, is lined with cylindrical epithelium and contains a large number of mucous glands. The upper or so-called olfactory portion is lined with ciliated epithelium, and is supplied, according to Todd and Bowman, with long, straight, tubular glands. Here the lymphatics are but poorly developed, while in the inferior portion they are very numerous; all their openings communicate directly with the deep facial and posterior submaxillary lymph bodies. Thus it can be readily understood why the slightest irritation, by a nasal catarrh for instance, in a child produces a temporary or permanent swelling of the lymph nodes and why the nares should necessarily, by their multitude of toxin absorbing lymph follicles and ducts, be among the most dangerous localizations of diphtheria.

The *epiglottis* carries a layer of pavement epithelium of 0.2 mm. in thickness on its anterior superior surface, that on its posterior surface being from 0.06 to 0.1 mm. in thickness. The superficial layer consists of spheroidal or polygonal cells, the deeper is of cylindrical cells arranged perpendicularly to the surface. Near the insertion of the epiglottis, the polygonal cells disappear, the cylindrical occupy the surface, and are furnished with cilia 0.005 mm. in thickness. Beneath these there are round and oval cells in considerable number, so that the whole epithelial coating has a thickness of 0.5 mm. Ciliated epithelium is also found on the *false vocal cords* and in the ventricles of the *larynx.* Polygonal pavement epithelium forms the covering of the posterior surface of the pharynx, of the aryepiglottic folds, where the mucous membrane possesses, in addition, a heavy and lax submucous tissue, and of the true vocal cords. As one approaches the laryngeal ventricles and trachea, the previous coating is replaced by delicate ciliated epithelium. The mucous membrane in the neighborhood of the laryngeal ventricles is itself very loosely attached, exceedingly thin, and frequently thrown into folds on the vocal cords. Acinous glands are here abundant, being fifteen to twenty to the square centimetre, and arranged lengthwise. Around the ventricles they are very numerous, and their outlets are lined with cylindrical, rarely with ciliated epithelium. The true *vocal cords* are not supplied with glands of any kind.

The acinous glands have no lymphatics leading into them, but the latter may be seen in other parts of the mucous membrane of the larynx and in the submucous tissue. In fact, they are both large and numerous, and have the general character of lymphatics, as regards the endothelium in particular. In the epiglottis of the new-born they form but a single layer, in the larynx and trachea two layers, and in certain parts which are covered by a considerable amount of submucous tissue, there are even three layers. Innermost the lymphatics are arranged perpendicularly to the surface; outermost, horizontally.

The comparative absence or scantiness of lymphatics over the larger part of the surface accounts for the absence of constitutional symptoms in localized laryngeal diphtheria ("pseudomembranous croup"), and the extensive layer of pavement epithelium accounts for the persistence of membranes both on the epiglottis and in some parts of the larynx.

The mucous membrane of the *trachea* and *bronchi* contains more elastic than fibrous tissue, a moderate amount of lymph vessels, no lymph bodies, but an abundance of mucous glands, and is freely supplied with ciliated epithelium.

Among all the tissues and organs thus far spoken of, the elastic tissue, which is an important element in the formation of connective tissue, is least affected by chemical or organic influences. It is not present in the mucous membrane of the nose, but to a considerable amount in the buccal cavity, is very abundant in the walls of the lymph follicles of the tonsils, and predominates in the trachea. The influence of these anatomical conditions on the diphtheritic process must be very marked. It can easily be demonstrated that where the elastic tissue is prevailing, a resistance to diphtheritic impregnation is maintained for a long time, but when it has been forced to yield, there is a corresponding resistance to recovery.

It is the pavement epithelium that gives the easiest foothold to diphtheritic membrane. Where it is most abundant, the diphtheritic process can best settle and develop. That is why the tonsils, not from their prominent situation alone, but from the character of their surface also, are favorable to the reception and further development of an infection, and their elastic and connective fibres, when at last affected, are apt to harbor the process a long time. Ciliated epithelium, on the other hand, is not so liable to be invaded. It occupies a higher rank in the scale of animal formation, has a more complex function and a greater power of resistance; besides, it expels by its constant movements microscopic foreign bodies.

The presence of a large number of mucous glands impedes, as a rule, by the presence of the normal secretion, an extensive destructive action upon the tissues. The secreted mucus assists in removing epithelial masses, and even fibrinous exudations, from the surface. The underlying tissues themselves do not always take an active or prominent part in the process; the serum of the mucus penetrates the parts which are the seat of morbid deposits, and tends to predispose the latter toward maceration, and the mucous secretion raises mechanically the superjacent deposits from their bed. Thus it is that the deposits in the respiratory portion of the nasal cavities are frequently cast off through the nostrils, probably because they have been produced in excess; and in a similar manner, the membranes that have formed in the trachea are ejected in a semisolid condition through a newly made tracheotomic, or even the natural, outlet. The large number of mucous glands in a part of the larynx and in the whole trachea is unquestionably the reason why the lymphatic vessels of the mucous membrane, even where they are present in large numbers, are not influenced by the overlying loosened masses, and will not absorb; hence laryngeal and tracheal forms of diphtheria have a decidedly local character, and are mostly devoid of constitutional symptoms.

The *vocal cords* form the borders of the narrowest aperture of the air passages; they detain or retain foreign bodies, whether malignant or otherwise; they are covered with pavement epithelium which, as has been remarked, is the principal resting and breeding place of the diphtheritic affection. They have no defence furnished by muciparous follicles, and therefore if there is any part which is predisposed to a local diphtheritic infection it is certainly the vocal cords. That is why in the beginning of an epidemic of diphtheria, or when it is dying out, a local diphtheritic infection can still take place, and individual cases occur now and then with an almost insignificant power of infection. Such occurrences took place previous to the ubiquity of diphtheria forty years ago, and are still met with under the same conditions, giving rise to the so-called sporadic membranous croup.

On the other hand, the absence of acinous glands on the vocal cords must serve to a certain degree as a guard against the disease. Dry, atrophic, but at the same time uninjured and smooth conditions of the mucous membrane of the fauces tend to ward off an attack of diphtheria. A more or less moist or viscid condition of the surface is necessary in order that the infecting material may cling thereto. The comparative dryness of the vocal cords, however, considered by the side of the perpetually moist and uneven surface of the pharynx, would not appear so favorable to the deposition of foreign infectious elements. Thus there are certain conditions predisposing to, others antagonizing infection. They demonstrate, however, why laryngeal croup is more frequent in winter than in summer, in direct proportion to the greater frequency of laryngeal catarrh in winter than in summer. Diphtheritic membranes on the vocal cords are not easily cast off, for there are no subjacent muciparous glands whose secretion could wash them away. No general infection can arise from them, for they have no lymphatic vessels which could serve as carriers of the poison; furthermore, suffocation from a local cause occurs too early to enable the few neighboring lymphatics to absorb and transport the toxin elsewhere, in case the deposits should finally become macerated.

The comparative absence of the lymphatics and the paucity of blood-vessels explain why diphtheria of the tonsils has so mild a character. The large number and size of, as well as the direct communication of the lymphatic ducts of the Schneiderian mucous membrane with the lymphatic glands of the neck account for the dangerous character of diphtheria of the nose. However, direct infection, *i.e.*, the absorption of the poison into the body, is not always dependent on the lymphatics, for they have occasionally neither enough time nor the opportunity to use their power. For instance, in those cases of diphtheria of the nose in which early and slight epistaxis occurred, the poison appears to have been absorbed directly into the blood-vessels. Then we fail to observe the ordinary swelling of the neighboring glands of the neck, but the general symptoms are very rapidly developed. Usually, however, infection results through the lymphatics. The fluid contents of the tissues, or such particles or elements as are suspended therein, be they of a gaseous, chemical, or parasitic nature, are conducted to the lymph nodes and into the circulation. There may be, however, two impediments in the current. In the first place, the foreign material may be present in too large an amount to circulate with ease; the result will be stagnation and consequent irritation, either in the fascia propria or in the substance of the lymph nodes. By pressure, the capillary circulation becomes interfered with, proliferation ensues, the circulating lymph mingles with the white corpuscles from the lymph spaces, and the result is an abscess in the intra- or periglandular tissue. Or the foreign material is retained in the interior of the fascias, in the connective tissue, or in the dilated lymph vessels of the cortical substance. Thus fluids injected into the cortical substance have been found collected in the external portions of the lymph nodes, where it was impossible for them to be carried into the circulation. Hence the lymph nodes may serve as the receptacle of noxious elements which have circulated in the lymph current, with or without danger to the integrity of its tissues. In this manner a second attack of diphtheria may often find its explanation in the absorption of stowed-away poison; as we see in the case of syphilitic or other infections, which may either be stored in the lymph body unchanged and inactive, or if their presence prove irritating, give rise to speedy suppuration, and even elimination, provided the abscess be opened sufficiently and early.

Dissemination of Diphtheria.

Diphtheria is a contagious disease. It is usually transmitted from the sick to the well by the moist or dry discharges from the nose and throat of the sick person. This transmission may take place directly or indirectly in so many ways that it is not always possible to trace an individual case to its source. It is the multiplicity of mostly unknown modes of transmission which confuses and bewilders. The vulnerability of the young mucous membrane, the frequency of nasal and pharyngeal catarrh, the narrowness of the nose, the large size and softness of the tonsils, the frequent fermentation of food in the mouth, the sucking of the soiled little fingers, together with the influence of family disposition, which is more powerful in the young, the constant intercourse of children with each other in large families and in densely populated houses and districts, in schools and on playgrounds, the possibly long period of incubation during which the disease is contagious though giving rise to no symptoms, act as just so many predisposing causes of contagion; and the large number and size of the lymphatics in the young render every attack so much the more dangerous.

The very facts that diphtheria need not always be of the same type; that many cases of lacunar or follicular amygdalitis ("tonsillitis") are diphtheritic—that there are as many cases out of bed and out of doors as in bed and indoors; that, particularly in adults, diphtheria may last long and give rise to but few embarrassing symptoms, and that a mild case of diphtheria may, by contagion, produce very serious ones, render contagion by nursery maids and other domestics, by teachers, seamstresses, sick-nurses, workmen, factory girls, shopkeepers, barbers, and all other persons mingling with the many extremely easy. The vitality of the diphtheria germs is persistent, as is well known, and may extend over years. They cling to solid and semisolid bodies, are imported in milk, cling to walls and floors, to toys, to curtains, towels, clothing, and bedding which is so often kindly donated to the poor by the benevolent well-to-do when they wish to get rid of their own dangers. They stick to omnibus and carriage cushions, to car seats, to the either ready or custom made coat on one's shoulders near which one's baby will nestle—the very coat that is sold in Broadway palaces after it has been made in the pest-stricken tenement sweating shop. The very restlessness of our people, the frequency of moving into unknown and often infected quarters, is another cause of doubling the number of cases. There can be no doubt, besides, that many animals—horses, chicken, cows—have and spread diphtheria. Thus it appears that we ought to think twice, and indeed many times, before admitting among the causes of diphtheria new factors which cannot be proved.

"No contagion could be traced." That is the introduction to every wild and unproven theory of indigenous spontaneous generation. When a case of cholera breaks out in a village a thousand miles away from the coast, is there anybody in our time who looks after chemical poison in a well or filth on the roofs? We look for direct or indirect contagion from a tangible source. Why not so in diphtheria? In the *New York Medical Journal* of September 27th, 1886, I quoted from Isambert the case of a medical assistant who had nasal diphtheria many months, and then travelled half a year to get rid of the last remnants. He fully recovered; but how many deaths did he cause—going from railroad car to railroad car, from stagecoach to stagecoach, from hotel to hotel? How many may have been the physicians who searched in vain for the cause of the sporadic cases suddenly springing up in their towns, and the epidemics generated by them along the roads on which the luckless wanderer after his own health had strewn out his curses? Nobody suspected the traveller who left days ago, just as nobody may be able to trace every outbreak of cholera to the unknown person who carried it upon his person or in his bowels. Nor is this an isolated case of a long duration of diphtheria. Cadet de Gassicourt operated for laryngeal diphtheria after eighteen, twenty-three, and forty-three days. Sanné had croup patients who recovered after twenty-seven, thirty-two, and sixty days. I know of many cases of diphtheria protracted into the second or even the third month.

Golay reported the case of a boy of five years who had the diphtheria bacillus three hundred and sixty-two days. During this time he had three acute attacks of diphtheria and four injections of antitoxin. Golay draws the conclusions from his report (*Revue médicale de la Suisse Romande*, 1897) that a fortnight's isolation after the disappearance of the false membrane, as advised, is inadequate; he does not believe in recovery until three or four examinations for bacilli made in intervals of a week each have proved unsuccessful. He also finds that the presence of the bacillus in the throat does not interfere *per se* with the general health; also that the bacillus is apt to remain a very long time unless there is a complicating streptococcus infection. In this case he tried many local applications (Loeffler's included) in vain.

Such facts, pointing as they do to the ready communicability of diphtheria, have influenced my opinion from early times. I cannot see anything miraculous in the sudden appearance of a *bacillus diphtheriæ* or a *streptococcus* in a person *apparently* not exposed to it. During an epidemic there is *nobody not exposed* to it, and everybody is subject to it under favorable circumstances. The latter mean a fit condition of the human integument, either cutis or mucous membrane, which makes it liable to become a resting-place for the germ. That fit condition is a slight or severe wound, abrasion, denudation of the surface. As no healthy surface becomes erysipelatous in spite of erysipelas being epidemic ("erisipila non est sine vulnere," Galen), as Fehleisen's bacillus requires a sore, so diphtheria, being ubiquitous and waiting for a chance, will stick to a cutaneous wound, a stomatitis, a pharyngeal or nasal catarrh, and will rapidly multiply. A resected tonsil will thus be covered with a pseudomembrane within a day.

I have been quoted as favoring the sewer-gas origin of diphtheria, though (with the exception of a careless expression on page 50 of my "Treatise on Diphtheria") I always, since 1860, strenuously expressed my conviction of the communicability of diphtheria solely by contagion (direct or indirect). Jenner in 1861, Wilks in 1873, Thorne Thorne in 1893, expressed the same opinion. I believe it is the latter careful and most painstaking observer whose statements, together with the discussion on the subject contained in the *British Medical Journal* of 1893 and 1894, in which Wilks, Davis, Priestley, C. M. Jessop, and J. Bunting—in opposition to George Johnson, Parker, C. N. Allfrey, N. G. Warrey, and P. G. Marriott—favored the exclusive contagion theory, have done most to establish the latter forever in the minds of our British brethren.

The vitality of bacilli is remarkable. It is true that direct light kills them after a while; even diffuse light has a similar though slower effect. It is also true that they do not live outside the body so long as on the human mucous membrane, and that one observer (Spengler) did not find them after one hundred and twenty days, and others (Wright and Emerson) found few only on brushes, and none on clothing or on the finger nails. But Abel found them on children's building blocks after five months. They resist desiccation a long time, in membranes (Roux and Yersin, Park, Loeffler, Germano), in tissues (Loeffler, d'Epine et de Marignac), and in dust (Reyes, Germano). Rapid desiccation, even by means of sulphuric acid, does not injure their virulence, which is preserved the better (being protected against oxidation) the thicker the surrounding dust. The latter may be the vehicle of contagion. Moreover, weeks and months after an attack of diphtheria, bacilli have been and are constantly met with in the throat, nose, antrum, and middle ear. We should not forget that no number of negative observations can outweigh a single positive result. And we do know, those of us who have not forgotten the value of clinical observation, that the infection of diphtheria in bedding and in rooms, which harbored diphtheria a year previously, has started it again in newcomers after they had dwelt there long enough for incubation.

There is no origin for diphtheria except in contagion. Sewerage has nothing to do with it. In a paper published in the Transactions of the Third Congress of American Physicians and Surgeons (1894) I presented the following conclusions:

The atmosphere contains more or less specific disease germs, both living and dead.

They are frequently found in places which were infected with specific disease.

In sewer air fewer such germs have been found than in the air of houses and schoolrooms.

Moist surfaces—that is, the contents of cesspools and sewers and the walls of sewers—while emitting odors do not give off specific germs, even in a moderate current of wind.

Splashing of the sewer contents may separate some germs and then the air of the sewer may become temporarily infected, but the germ will sink to the ground again.

Choking of the sewer, introduction of hot factory refuse, leaky house drains, and absence of traps may be the causes of sewer air ascending or being forced back into the houses. But the occurrence of this complication of circumstances is certain to be rare.

Whatever rises from the sewer under these circumstances is offensive and irritating. A number of ailments, inclusive perhaps of sore throats, may originate from these causes. But no specific diseases will be generated by them except in the rarest of conditions. For specific germs are destroyed by the process of putrefaction in the sewers, and the worse the odor the less is the danger, particularly from diphtheria.

The contributing causes of the latter disease are very numerous, and the search for the origin of an individual case is often unsuccessful.

Irritation of the throat and nasopharynx is a frequent source of local catarrh; this creates a resting-place for diphtheria germs, which are ubiquitous during an epidemic, and thus an opportunity for diphtheria is furnished.

Of the specific germs, those of typhoid fever and dysentery appear to be the least subject to destruction in cesspools and sewers. These diseases appear to be sometimes referable to direct exhalation from privies and cesspools, but very few cases, if any, are attributable to the action of sewer air.

The impossibility or great improbability of the infection of specific diseases, except dysentery and typhoid fever, rising from sewers into our houses, protected as they are, or ought to be, by good drains and efficient traps, should, however, not lull our citizens and authorities into indolence and carelessness. For the general health suffers from chemical exhalations, and the vitality of cell life and the power of resistance are undermined by them.

SYMPTOMATOLOGY.

Prodromes.

After an incubation period lasting from a few hours to fourteen days, prodromi may precede the chacteristic symptoms of diphtheria from a few hours to several days; some of them are identical with those of other infectious diseases. They are lassitude, headache, general malaise, and nausea; occasionally vomiting, seldom diarrhœa, more commonly constipation; universal muscular sensitiveness, and some stiffness of the neck. The throat is complained of by older children as being dry; the mouth is easily opened, there may be no discoloration of the fauces, or a hyperæmia only which, as if it were traumatic, may be quite local. The tonsils and pharynx are seldom sensitive to the touch, but the swallowing of fluids is rather difficult. In those cases in which a swelling of lymph bodies is noticed near the angle of the lower jaw at this early period, there is pain on pressure. The temperature is seldom raised except in these cases; in them nervous symptoms are observed, such as chills and convulsions. There is rarely a short pharyngeal cough, still less frequently a hoarse voice, or dyspnœa, or laryngeal stridor.

Symptoms.

The Throat.—Most cases of diphtheria begin in the throat. The tonsils being large in the young, and exposed to superficial lesions occasioned by catarrhal processes, and to injuries of the epithelium (during deglutition), are most readily invaded by bacilli and other microbes. There may be no, or a slight, or a high elevation of temperature. This difference, like all other symptoms, depends on the various degrees of virulence of the invading microorganisms, on the condition of the invaded tissue, on a greater or lesser degree of previous immunity, and on the different powers of resistance on the part of the patients. When the temperature is high (104°–107°) there may be a convulsion, or vomiting, or sometimes diarrhœa. But these symptoms of the initial stage are rare.

The throat is red, all over in most cases, or locally; mostly on the tonsil, or near it, there is a grayish or whitish spot, the size of the head of a pin, or larger. Sometimes the first inspection reveals the presence of a membrane of the same color or brownish. The small grayish spot will increase within a few hours or a day until it grows into a membrane, or there are more than one, four or six or more, which soon coalesce. The membrane may be thin like a film, or thick; lying rather loose on the mucous membrane, or tightly adhering so that its removal is difficult and attended with a little bleeding; when it is removed it is reproduced in a few hours or half a day. The grayish discoloration is not always membranous; quite frequently it is caused by an exudation into the tissue and cannot be removed at all. Then it does not come away at any time but undergoes a process of necrosis, and if it heals at all does so only by healthy granulations springing up on the ulcerating surface. The neighboring tissues, mainly the uvula when it is covered with membrane, become œdematous and may swell considerably. Then deglutition, respiration, and articulation may suffer accordingly. At first the membrane has no odor. In bad cases, and after some days, when maceration begins, there is some odor, which may be very offensive and fetid in septic cases. In the neighborhood of the membranes the lymph bodies will swell, the region of the tonsils becomes painful on pressure, and there is some, or much, swelling, which depends in part on the tumefaction of the lymph bodies alone, and in part on that of the surrounding loose tissue. The face is pale and sallow, may be bloated even in mild cases, and its expression is liable to be that of indolence and apathy; in bad cases of sepsis and when the veins of the neck are compressed by exudation the color may become livid. There are but few mild cases of uncomplicated diphtheria that do not exhibit some constitutional symptoms; the pulse becomes a little frequent and small; in bad cases it is very small, very frequent, or very slow. Those cases in which the pharyngeal diphtheria spreads into the nasopharynx, nares, or larynx have their own additional symptoms; they will be considered below, so will be those which terminate in destruction of tissue in the throat in consequence of deep ulceration and gangrene, which may even result (though that occurrence be rare) in perforation of the soft palate, or its adhesion to the posterior wall of the fauces.

The local symptoms of diphtheria may be very indistinct, even absent. As early as 1860 I described cases of diphtheria without membrane, this being absent either in the first stage only or altogether. At the present time the bacteriological proof corroborates what I then had ample reasons to conclude from clinical facts. The term catarrhal diphtheria has been accepted by many since, though it has been combated by others. That such cases may occur in families in other members of which well-authenticated instances of diphtheritic membranes are met with has been substantiated by many, among whom I am glad to count Baginsky. To call such cases "masked diphtheria" appears unjustifiable, so long as the diagnosis is made, as now, by the presence of the bacillus and of acute surface changes in the mucous membrane.

Diphtheria may, and frequently does, present itself, with its solitary dots on the tonsils, in the form of follicular or lacunar angina. Long before the advent of a bacteriological diagnosis that fact became clear to me. Still the numerical percentages of such cases will change even according to seasons and epidemics.[*]

This follicular form of diphtheria is often noticed in adults, and is a frequent cause of communication of the disease, the more easily as adults are less liable to suffer from constitutional symptoms. But I never said what I have been charged with, that diphtheria is spread by adults suffering from follicular amygdalitis (tonsillitis). On the contrary, what I did and do say is that what was called in an individual case by that name and then gave rise to diphtheria, was diphtheria, and therefore caused diphtheria. Nor do I say that every case of follicular affection of the tonsils is diphtheria, and that diphtheria in general is spread by follicular amygdalitis in general, but I claim that this name is too often only a cloak for the lack of a correct or complete diagnosis. "Follicular" and "lacunar" are adjectives describing a locality, nothing else. There are cases of a follicular or lacunar amygdalitis of a catarrhal, a purulent, a fibrinous, and a diphtheritic character, and the name ought to be dropped from our nomenclature, because it gives rise to mistakes unless it be complemented with a descriptive adjective (*Medical Record*, November 27th, 1886). This variegated condition of the tonsils and pharynx was also described by me in an article "On Diphtheria and Diphtheritic Affections," in the *American Medical Times*, August 11th and 18th, 1860, and in C. Gerhardt's "Handbuch der Kinderkrankheiten," II., 1877.

The follicular form of amygdalitis (diphtheritic or other), causing local and small circumscribed alterations only, may easily be mistaken for a similar circumscribed deposit which is not in a tonsillar lacuna, but on some other part of the tonsil. This punctated diphtheria is mostly seen in larger children, in adolescents, and in adults, for the reason that renewed attacks of pharyngeal inflammation so harden and cicatrize the tonsillar surface that extensive exudations can no longer take place. The broad statement is justified that pharyngitis creates a disposition to diphtheria and to the formation of large membranes in the very young, and rather destroys it or causes only small exudations in advanced age. But whether membrane or dot, they are equally contagious. A mild variety begets that which is mild or severe, as the severe form may produce its like, or a mild variety. This mild variety is that from which adults are apt to suffer. It made me proclaim the warning that there is as much diphtheria out of doors as indoors, as much out of bed as in bed. With this variety the adult is on the street, engaged in business, in the schoolroom, in the railroad car, in the kitchen, and in the nursery. With this variety parents, while complaining of slight throat trouble, which is not heeded, kiss their children and infect them (*Medical Record*, November 27th, 1886).

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[*] If Edmund Meyer's 55 cases of "typical" angina lacunaris gave him staphylococcus aureus in 15, a mixture of staphylococcus and streptococcus in 24, streptococcus pyogenes in 14, and Klebs-Loeffler bacillus in only 2 instances, he had an experience different from those of Lennox Browne, Koplik, and Feer ("Aetiologische und klinische Beiträge zu Diphtherie," 1894, p. 43). The latter should hold himself responsible for the following words literally translated: "It is an *established* fact that many cases of lacunar anginæ *are* of diphtheritic origin, though Jacobi's opinion, according to which that is so, has become *untenable* through bacteriological research."

The confusion in regard to the accurate diagnosis of an individual case is caused by the difficulty of always establishing the temporary presence or absence of the Klebs-Loeffler bacillus. Having noticed the frequent identity of lacunar "tonsillitis" with diphtheria, C. Fraenkel, E. Czaplewski, and others "believe" that bacilli are actually more common than is generally assumed, and that numerous alleged cases of streptococcus pseudodiphtheria are, after all, caused by the bacillus, and that, on the other hand, uncomplicated bacillary diphtheria is quite rare.

Another cause of confusion was the assumption that genuine bacillary diphtheria was the most dangerous form of the disease. There was a time when the diagnosis of diphtheria was made by the omniscients from the termination of the case: if the patient died, it was diphtheria; if not, not. The advent of the bacillus has changed that; the bacillus case is at once made out to be the most dangerous and fatal case. Nothing is more erroneous. As a rule the uncomplicated bacillus case is not among the fatal cases; as a rule the uncomplicated streptococcus case is not fatal; but the mixed case is ominous. The elimination or non-appearance of one of these components is a favorable occurrence. The latest illustration of this fact is the report of Strassburger, who states that the large majority of diphtheria sufferers in Bonn carried Klebs-Loeffler bacilli which were comparatively harmless. These mild cases were not complicated with streptococci, which were present in every grave case.

Skin.—An erythematous eruption, more or less general, appears sometimes on the skin immediately with the invasion of diphtheria, or after a few days only. It is either evanescent, scarcely visible for more than a few hours, or covers a large surface and remains some days. It has been mistaken for scarlet fever, but is not generally attended with a high temperature and with the intense stomatitis and glossitis of scarlatina; by the lower temperature it is also distinguished from the erythema which is liable in predisposed infants or children to accompany many feverish diseases.

This eruption of diphtheria does not appear to be proportionate to the seriousness of the illness. At all events it has nothing in common with erysipelas, which, however, is apt to accompany such cutaneous diphtheria as follows abrasions of the skin, and is found on tracheotomy or other wounds. Such local deposits of diphtheritic membranes are often found on the local denudations of scratch wounds, eczema sores, or vesicatories. They are apt to remain local; but, on the other hand, in many cases in which the first localization of diphtheria is in the skin, it will affect the neighboring lymph bodies and infect the whole body. As a rule, however, it is amenable to early and effective treatment, and that is why Trousseau declared most cases of cutaneous diphtheria to be devoid of danger.

In connection with these cutaneous alterations may be mentioned the more or less local or general emphysema which occurs sometimes during or after tracheotomy. I had that disagreeable experience a number of times, on account of my preferring to operate mostly below the thyroid gland. There the mediastinal tissue is sometimes injured, and during the intense dyspnœa a local emphysema of the subcutaneous tissue is the instantaneous result. Even from a slight rupture of pulmonary alveoli much air will escape and the whole body may become transformed, as it were, into a bulging, crepitating balloon.

Extensive œdema is sometimes noticed, even without albuminuria.

In connection with the alterations of the skin petechiæ, purpura, and ecchymoses may be mentioned, though indeed they might find their proper place also under the head of the organs of circulation. Like scarlatina and still more measles, and indeed all infectious diseases, diphtheria (principally the mixed bacillus and streptococcus infection), mainly when the myocardium is altered and when blood-vessels are obstructed, will result in effusion and either small or large extravasations. Beside the latter in its different forms urticaria, erysipelas, and variola-like eruptions will be observed. There is, however, no eruption that is pathognomonic of genuine diphtheria.

The local lesion of the mucous membranes gives rise to bloody discharges from the nares or the pharynx. When sepsis is very intense and gangrene deeper, actual hemorrhage will occur. The large majority of dangerous or fatal hemorrhages come from tracheotomy wounds, now and then perhaps from mere pulmonary hyperæmia and apoplexy, sometimes after the loosening of membranes, or from erosion of larger blood-vessels. Now and then the pressure of an improper tracheotomy tube would cause it, as in Ganghofner's and in Maas's cases of hemorrhage from the innominata, sometimes the septic destruction of a carotid artery, as in a case described by me (Transactions of the Association of American Physicians, 1898), or that of other large blood-vessels would lead to a fatal termination from profuse bleeding.

Nose.—The diphtheritic membranes spread quite often from the throat to the nasal cavities, mainly when the posterior aspect of the uvula is affected. The latter's frequent contact with the posterior wall of the pharynx during deglutition exposes the posterior wall of the pharynx as well. In many such cases the membrane is very thick and dense, and apt to obstruct the nasal passages sometimes to such an extent as to close them entirely. Usually there is no or very little nasal discharge; but articulation becomes "nasal" and the voice "thick" very soon, and respiration is hampered. The deep facial lymph bodies near the angle of the lower jaw are more or less swollen. Whenever they are so, the nasopharynx should be examined.

Primary diphtheria of the nose (diphtheric or diphtheritic rhinitis) is of frequent occurrence. Either without any prodromi, or during or after an acute or a chronic nasal catarrh, with much or with little discharge, there is a thin, serous, or slightly flocculent secretion which is more or less profuse, sometimes not, sometimes slightly, other times intensely fetid. Hence, during the prevalence of a diphtheria epidemic, every nasal (or pharyngeal) catarrh requires immediate attention. This primary form may also lead to the exudation of thick membranes, as described above; the general consecutive symptoms so much to be dreaded do not depend, however, on the thickness of the membranes. On the contrary, in many cases with only thin membranous deposits the lymph bodies are more affected, and the effect of the toxin becomes painfully visible in the either very slow or rapid and feeble pulse with all the other symptoms of a generalized sepsis. The cervical adenitis has but little tendency to suppuration; but a gangrenous degeneration takes place mainly in the mixed infections, or chronic hyperplastic infiltrations tell their tales for years to come. There is no more dangerous form of diphtheria than that of the nares. Still more, however, than the foul-smelling cases are to be feared those which exhibit few membranes, but at an early period a sanguinolent discharge. In these not even the lymph bodies may swell, but absorption will take place directly through the blood-vessels, which are open, as is proved by the very presence of blood in the discharges.

So long as the final clinical diagnosis of diphtheria depends on the presence of the bacillus, if found, in the membrane or in the discharge, the numberless papers strutting about the magazines to prove either the innocuousness or the dangerousness of fibrinous rhinitis, or again the presence or absence of bacilli in fibrinous rhinitis, or its ability or inability to cause faucial or laryngeal diphtheria, are superfluous vaporings of single observations. Whenever nasal diphtheria is diagnosed in any of its forms, or even strongly suspected, danger should be assumed to exist. In most cases the infection is mixed, very mixed. Edmund Meyer (*Archiv für Laryngologie und Rhinologie*, IV., 1896) found in twenty-two cases of "fibrinous rhinitis," nine times streptococci and staphylococci albi and aurei, and thirteen times Klebs-Loeffler bacilli; Guarnaccia, in his cases of "caseous rhinitis," found Klebs-Loeffler bacilli, streptococci, staphylococci aurei and albi, sarcina lutea, bacillus subtilis, bacillus proteus, leucocytes containing microbes in their nuclear protoplasm, and streptothrix alba.

The *conjunctiva* of the upper (more frequently) or the lower eyelid becomes diphtheritic either primarily or secondarily (when the nose and lacrymal ducts are primarily affected). Diphtheritic conjunctivitis is not a frequent disease—sometimes I do not see a case in a year; thirty-five years ago it was frequent and destructive. Evidently the epidemics differ in regard to virulence. Usually the membrane spreads rapidly from one eyelid to the other; when the palpebral conjunctiva is smooth, dry, and pale while that of the bulbus is chemosed, the whole lid becomes red, swells and stiffens, and a membrane is first deposited in floccules, which soon coalesce into solid masses. These are so thick as to press upon the cornea, which speedily becomes hazy and ulcerates. Perforation takes place, the iris prolapses, and sometimes the eye is destroyed within a single day. It takes the membrane a few days to begin maceration.

The accurate diagnosis of the character of the membrane should be made in the usual way; in many cases simple film preparations, to the exclusion of cultivation, are sufficient. It is claimed by Moray (*Annales d'oculistique*, April, 1895) and Sydney Stevenson (*British Medical Journal*, June 18th, 1898) that quite often the discharge from the eye contains only that microbe which is the cause of the inflammation. There is only one source of confusion likely to arise, viz., that between Klebs-Loeffler and xerosis bacilli.*

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* The main points of distinction are (according to Stevenson): 1. Both stain by Gram's method, but the diphtheria organism loses its gentian violet, when in alcohol, much more quickly than the xerosis bacillus. 2. Klebs-Loeffler bacilli give rise to an acid reaction when grown in neutral bouillon or milk, while xerosis bacilli never do. 3. The latter, when inoculated into guinea-pigs, cause nothing more than a swelling at the site of the puncture.

According to Ammann[13] the cornea may be affected by the Klebs-Loeffler bacillus alone, but is mostly invaded only when strepto- and staphylococci are present. Once he found non-virulent bacilli together with the virulent.

The *ear* is liable to take part in the diphtheria of the nasopharynx. Membranes may continue into the funnel-like aperture of the Eustachian tube, which in the young is relatively larger than in the adult, or the specific catarrh (a mere surface diphtheria) may extend into the middle ear. Since I collected what little literature there was in 1880 ("Treatise," p. 75), instances of that kind have multiplied. The drum membrane, the external meatus, and the lobes are subject to diphtheria when the surface epithelium has been injured. A complication with erysipelas I saw thirty years ago on the external ear of a newly born child; in older children I have seen that same unfortunate complication during bad epidemics; also, without erysipelas, a gangrenous disintegration of the cheek, of the external ear, sometimes down into the bones, with all the possibilities arising in the various forms of otitis media and ostitis. While some died of sepsis, others would succumb to thrombotic obstructions of a sinus.

The *kidneys* are liable to participate in most infectious diseases, even in the common forms of pharyngitis; in none more so than in diphtheria, no matter whether mild or grave. Evidently the irritation caused by the elimination of the toxin damages either merely the functions or the substance of the kidneys. Albuminuria is seen early, about the third or fourth day, even on the second, in perhaps one-third of all the cases, while the quantity of the urine is rarely diminished, sometimes increased. Blood there is very rarely, even in septic cases less frequently than in scarlatina. Urea is present in normal or fair quantities, and the salts are nearly normal. Cylindroids (mucin) and sometimes hyaline casts are found in these simple cases in which the albumin may be present a few days or a week, without exerting an influence on either the temperature or the other symptoms. Sometimes, after having been quite copious, it disappears very suddenly.

The xerosis bacillus is believed by Schanz to be identical with the Klebs-Loeffler. Its microscopical features vary, but not more so than those of the latter and of the "pseudobacillus." It differs in this also that, though it is always combined with streptococci, it is not believed to be virulent, inasmuch as it does not cause diphtheria. Still, there is a case of von Hippel—examined by C. Fraenkel also—which proved the virulence of the xerosis bacillus. It was met with in the conjunctival sac of a man who had been operated upon for cataract. It was found to be very virulent in animal experimentation, though on the eye of the patient there was no kind of inflammation, least of all diphtheria. The absence of diphtheria, however, in the presence of Klebs-Loeffler bacillus on mucous membranes is a frequent occurrence.

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COLLEGE [illegible]

Actual nephritis is not so frequent as in scarlatina, but it occurs. Hyaline casts in larger numbers, turbid cells, small granular casts are the first microscopical symptoms, which may be followed by large granular casts and occasionally only a few red blood cells. The urine becomes scanty, the skin more pallid, the collapse more intense. In this nephritis of diphtheria there is less œdema, less dropsy, less uræmia than in that of scarlatina or other complications. Convulsions are not even so frequent in this stage as they may be in the incipient stages of such cases as begin suddenly and with a high temperature. The patients die, now and then, without losing consciousness to their last hour. A fatal termination is not so common as in other complications. When albumose is found, together with considerable albumin, Berlin (*Münchner medicinische Wochenschrift*, No. 42, 1897) believes the prognosis to be rather favorable. Still in most of the cases at the clinic of Strassburg in which he made his observations, the renal complications were only trifling.

The *bronchi* and the *lungs* participate in various ways and at various times. The pseudomembrane, whether streptococcic or bacillary, descends into the ramifications of the air tubes, or it is first formed in these, where it may become localized or whence it may ascend. This "fibrinous bronchitis" may run a rapid or a slow course. After the pseudomembranes have been thrown off, a mucopurulent inflammation may remain and prove dangerous to the exhausted patient. Pulmonary œdema, with intense bronchial hyperæmia and extensive dilatation of the blood-vessels, results from the rarefaction of air in the lungs during laryngeal obstruction. This form can be best observed during a tracheotomy when it is made after a long duration of stenosis; an incredible amount of œdematous fluid will ascend from the trachea under such circumstances. The intense bronchitis accompanying it is frequently the forerunner of elevations of temperature and of bronchopneumonia within one or two days. Broncho- or fibrinous pneumonia may also follow the aspiration of membrane (as well as of food) during dyspnœa. The microbic nature of the membrane determines frequently the microscopic character of the consecutive pneumonia, which may be simply pyococcic but appears to be mostly attended with or caused by the Klebs-Loeffler bacillus (Wright, Kanthack, Stephens, Flexner). In the septic form, or under ordinary circumstances also, a gangrenous pneumonia has been observed. Most pneumonias observed in diphtheria accompany, or are dependent on, the laryngeal form (croup). That is why percussion and auscultation do not yield so conclusive results in such cases; for dulness may be found over a merely atelectatic area, and the respiratory murmurs are obscured by the transmitted sawing, loud, laryngeal sounds. Still when the hitherto low temperature is replaced by a high one, and the normal long-drawn inspiration of uncomplicated laryngeal diphtheria (croup) gives way to great frequency of respiration, the suspicion pointing to pneumonia becomes almost a certainty.

Like strepto- and staphylococci the Klebs-Loeffler bacillus is found in tuberculous lungs. It is easily seen that, as it is frequent on the mucous membranes of the upper part of the respiratory organs, it may readily appear in its lower distributions. Whether it modifies the tuberculous disintegration remains an open question. The influence of the streptococcus on the tuberculous process is assumed by all to be powerful for evil. While it is possible and appears to be proven that the presence of streptococci interferes with the growth of Klebs-Loeffler bacilli, other observations have shown that under certain circumstances the non-virulent bacilli may become virulent under the influence or in the presence of streptococci (Schütz in the *Berliner klinische Wochenschrift*, April 18th, 1898).

The *œsophagus* rarely participates in the diphtheritic affection of the pharynx beyond a distance of from 2 to 3 cm. where its tissue is healthy. If it is not healthy, for instance near cicatricial contractions, membranes may be found at any place. They may be deposited loosely on the mucous membrane and easily floated, or may be embedded in the tissue, and then lead to necrosis.

The *stomach* participates in the symptoms of incipient diphtheria by vomiting, which, however, is not frequent. Gastric pain and vomiting may precede cardiac paralysis. Membranes, however, are found in exceptional cases only. In one I concluded they were swallowed before death. The *intestinal tract* has diphtheritic (dysenteric) membranes in the rectum and colon, sometimes in connection with pharyngeal (and nasal) diphtheria. Mixed (bacillus and streptococcus) infections are sometimes complicated by a septic diarrhœa with gangrenous fœtor, and at the same time with purpura, nephritis, and intestinal hemorrhages. Schwabe has reported the case of a physician who died of a septic diarrhœa contracted by swallowing membranes aspirated from a tracheotomy wound.

The cases of diphtheria of the *bladder*, *vagina*, and *penis* recorded by me in my "Treatise" of 1880, pp. 86–90, do not bear perhaps the present test of bacteriological diagnosis. But several cases, so verified, of diphtheria of the vagina and of circumcision wounds have been seen by me since. One of the former was met with in a case of nasopharyngeal diphtheria, two of them were followed by a faucial affection, one of these was puerperal. The inguinal lymph bodies were not much affected, but a slight swelling I never missed. One patient with diphtheria of a circumcision wound, neglected and gangrenous, died with large inguinal adenitis. Nisot, Bumm, and J. Whitridge Williams (*American Journal of Obstetrics*, August, 1898) report cases of diphtheria of the vagina (and uterus). In the case of the latter the woman was (possibly) infected by the physician. Her new-born baby and several other children caught the disease from her, and the baby died.

There is rarely a case of diphtheria in which the *lymph bodies* in the neighborhood of the diseased locality are not affected. The latter determines the swelling which is to take place. Previous remarks explain why a diphtheria limited to the tonsils does not cause much swelling of the lymph bodies, or why that of the vocal cords when uncomplicated exhibits no secondary adenitis at all, and why a nasal diphtheria with sanguinolent discharge from open blood-vessels, though constituting a formidable variety of the disease (the toxin being introduced directly into the blood circulation), should show no tumefied lymph bodies. These are irritated by the absorption from the diseased surface, the swelling corresponding both to its locality and the gravity of the case. Bacillary diphtheria, not or but little complicated with streptococci, shows less adenitis than when the affection is thoroughly mixed. Simple streptococcic membranes yield more adenitis than a mild bacillary diphtheria. That is why so many cases of scarlatina in which the complication with streptococci is more frequent than that with bacilli, have more faucial and cervical tumefaction than diphtheria. Suppuration is less common in the Klebs-Loeffler affection—Lennox Browne's opinion notwithstanding—than in the streptococcic or in the mixed affection. Large abscesses are not frequent. Though the swellings be ever so immense in mixed infections, they do not abound. There may be many of them, but they are mostly small. The degeneration which takes place is rather a necrosis and gangrene than suppuration.

The seat of the adenitis corresponds with that of the diphtheria. The posterior nares correspond with the deep-seated lymph bodies below and near the angle of the lower jaw to such an extent that this diphtheria, though no membranes be visible, may thus be diagnosticated. In very grave cases the swelling will even extend to the parotid.

The *heart* is probably affected in every case of diphtheria. In Gerhard's "Handbuch der Kinderkrankheiten," Vol. II., 1877, I mentioned the symptoms with their anatomical foundation which I characterized as extravasations, cellular and nuclear alterations (myocardial), and endocarditis, first mentioned by Bridges. Among 17 autopsies recorded by Reimer there was fatty degeneration of the heart in 6, and ecchymosis of the myocardium in 3 cases. In addition to frequent hyperæmia of the abdominal viscera there were emboli of the liver in 3, with capillary hemorrhages in its peritoneal covering in 1, and emboli in the spleen in 5 cases.

The symptoms do not always correspond with the tangible anatomical changes. The results of the thousands of anatomical and microscopical examinations which have been made these forty years, though they be insufficient to explain the physical foundations of the morbid symptoms, do not justify the establishment of a "diphtheritic fever," which I resorted to in 1860 for the purpose of classifying just such cases in which the symptoms did not appear to be based on palpable changes. There is no case ever so mild apparently that will not affect the heart's function at once to a certain extent. From mild cases to the gravest there are gradual transitions. The skin is pale, yellowish, livid, cyanotic, sometimes the lividity and cyanosis are quite localized, the pulse is feeble, mostly frequent; in bad cases sometimes slow, often irregular and intermittent; in the worst cases filiform when near or over 200, apparently of normal volume (still compressible) when quite slow (30-50), sometimes dicrotic, or galloping. The heart is sometimes still more irregular than the arterial pulse. Its transverse diameter is enlarged, mainly over the right ventricle; the sounds are muffled and drawn out, and in this way audible over a large surface. Real bellows murmurs, when localized, are met with in endocarditis only. The complex of symptoms belonging to actual parenchymatous myocarditis will generally not set in before the end of the first week. Turbidity of cell structure, fatty or waxy degeneration, and loss of cross striation are the anatomical changes which have been verified hundreds of times; they correspond to a certain degree of cardiac incompetency and are probably due to the influence of the diphtheria toxin only.

Mollard and Regaud (*Annales de l'Institut Pasteur*, 1897) found affection of the myocardium, together with changes in other viscera, in every one of their eighteen cases of experimental diphtheritic intoxication. Occasionally it was confined to the muscular tissue, which became abnormally striated and sometimes, through disintegration of nuclei and protoplasm, was destroyed. Others report the presence of numerous nuclear alterations in the cardiac muscle (Kretz), another (Hibbard, Boston City Hospital, 1898) "in the vagus some evidence of degenerative changes."

The *liver* is enlarged and easier to feel than the spleen. Its size and resistance may increase tremendously when the circulation becomes sluggish under the influence of general exhaustion and sepsis, and of myocardial changes. Jaundice is met with in very grave and septic cases.

The *spleen* is enlarged in most cases, but difficult to palpate because of its softness, and to percuss because of the tympanites which frequently attends the disease. Even under normal circumstances the percussion of the spleen in the very young is not a successful procedure.

In Reimer's cases the *blood* was frequently normal, very often watery and dark, at times leucocytotic; the latter condition was also noticed by Bouchut and Labadie-Lagrave. Wunderlich reported two cases of Hodgkin's disease which developed during diphtheria; Bouchut and Dubrisay found leucocytosis with considerable disproportion in the number of red and white cells, which, however, was not great enough to justify the diagnosis of leucocythæmia. Many examinations of the blood have been made since, all with similar results. Thus Gabritchevsky found hyperleucocytosis in every case of diphtheria. It is greatest in fatal cases; during convalescence and after the injection of antitoxin it diminishes. A progressive hyperleucocytosis in diphtheria justifies a bad prognosis, and the analysis of the blood gives useful information regarding the value of treatment. Ordinarily the white cells vary between 11,450 and 25,000, and in fatal cases between 29,500 and 51,000. J. L. Morse, who quotes Gabritchevsky, comes to similar conclusions (Boston City Hospital Reports, 1895).

The *nervous system* is profoundly affected by diphtheria. During the first days of a pharyngeal diphtheria the soft palate may so swell as to interfere with respiration and deglutition. In most cases an improvement will take place with the restitution of the tissues to a fairly normal size, and the local paralysis will be only apparent. In other cases this apparent paralysis may change into an actual one in the second or third week or later. Usually, however, the difficulties of respiration and deglutition are moderate—indeed, paralysis is liable to follow apparently mild cases in preference to those which exhibit a vast amount of pharyngeal exudation—and after convalescence has actually set in or progressed for some time a peculiar array of symptoms will make its appearance. Usually the paralysis begins in the throat, the uvula appears elongated, the soft palate becomes gradually immovable, articulation is nasal, deglutition becomes difficult, fluids instead of being swallowed may be discharged through the nose, or, when the muscles of deglutition are becoming paralyzed, run down the larynx and cause cough and pneumonia. This paralysis of the soft palate is mostly bilateral, sometimes unilateral. A week or two after the beginning of the pharyngeal paralysis, often while it is getting better, the accommodation of ocular movements becomes faulty in consequence of a symmetrical paralysis of the ciliary nerves (Eulenburg). Paralyses of the internal and external rectus are less symmetrical. The pupils are not affected, other branches of the motor oculi and the abducens but rarely. Total ophthalmoplegia has been observed in a few cases only. After thousands of similar observations have been made, the observations of Scheby-Buch are still classical. Of 38 clinical cases of paralysis of accommodation 24 resulted from diphtheria; of these 20 were located in the throat, 3 started from wounds, 1 from the vagina, 1 from the skin. There was no mydriasis, with one exception. Refraction, which was invariably diminished, and vision, which was slightly impaired, became normal again with the restoration of health. This paralysis of accommodation was complicated with paralysis of the palate in 10 cases, in 9 cases it was uncomplicated, as in many other instances noticed before and after Scheby-Buch. Sometimes it would occur several or many weeks after the appearance of the pharyngeal paralysis.

Next in the usual order is paralysis of the muscles of the trunk and of the upper and lower extremities, frequently preceded by paræsthesia or anæsthesia of some or all the fingers and the palm (and other parts) of the hands and feet, also of other parts of the surface. These affections of the sensitive nerves may be quite local. I have met with anæsthesia of the trunk. Even the sensory nerves may become paralytic, the organ of taste in a case of Magne's; more instances may be found in my "Treatise," p. 101, in some of which the sensitive changes were such as to cause ataxia. The temperature sense has been found diminished sometimes. The motor paralysis of the extremities may increase until the limbs are entirely useless for weeks; as a peculiar mitigation may be mentioned the comparative immunity of the fingers in many cases.

The sphincters of the bladder and of the anus are rarely affected, likewise the muscles of the larynx and the respiratory muscles. When both the external respiratory muscles and the diaphragm are mildly taken there is cough, flapping thoracic respiration, and some dyspnœa. In severe cases the patient dies of apnœa, sometimes suddenly. Peristalsis is rarely paralyzed; but a single case of extreme constipation has come to my notice, and Baginsky, with his ample opportunities for observation, has seen a few only. Hemiplegia is found but rarely, and scarcely at all in the very young. One such case has been published by J. W. Brannan. This writer says: "There are thirty-five cases in all recorded in medical literature of postdiphtheritic paralysis of cerebral origin. Six cases have come to autopsy; in one of these a hemorrhage was found in the internal portion of the lenticular nucleus, with destruction of the neighboring part of the internal capsule. In the other five cases there was embolism of the Sylvian artery. . . . In the total thirty-six cases there was complete recovery in four, death in seven;

in all the others there was permanent paralysis of greater or less extent."

A case of acute disseminated sclerosis of the spinal cord, with neuritis, in diphtheria has been recorded by S. G. Henschen (Berlin, 1896).

The peripheral nerves act according to no rule. Sometimes the knee reflexes are diminished or absent early, at other times late. Reaction of degeneration is quite common in advanced cases, but will disappear in the course of the general recovery.

In the beginning of a diphtheria the prediction that paralysis will follow or not cannot be made. The very worst cases may be spared, mild ones will often be followed by paralysis; the latter fact has been substantiated in certain experiments made by Heubner. The location of the diphtheritic process is indifferent in regard to paralysis; it was found twenty-five years ago by Gaytton, Scheby-Buch, and myself, also by Maingault (1854, 1859), who deserves the credit of having added most (after Bretonneau) to our acquaintance with diphtheritic paralysis, to be connected with diphtheria of the genital organs. The cause of paralysis is not local, but general and toxic. In some seasons and epidemics the percentage of diphtheritic paralyses is quite high (ten to thirty), in others low; that is why the figures belonging to a long series of consecutive cases only should be considered. Now and then the order in which the symptoms of paralysis follow each other is not disturbed; but sometimes precisely the contrary holds good. Indeed in many seasons it is characteristic of diphtheritic paralyses to follow no certain course, passing by some parts of the body and attacking others.

The unexpected occurrence of sudden death in diphtheria has sometimes been discussed in connection with the nervous system, at other times with the heart. At all events it is the result of a cardiac paralysis, due to a change either in the ganglia or in the pneumogastric or in the sympathetic fibres. My first case of the kind was observed in 1857 and described in Gerhardt's "Handbuch," II., also in my "Treatise," p. 94. No explanation was found at the autopsy. It occurred before Zenker, Hiller, and Mosler described parenchymatous inflammation and granular degeneration of the heart muscle, and before the anatomical causes of defective or interrupted innervation were the subject of much study. Afterwards those changes described by Zenker in connection with all sorts of infectious and feverish diseases, also amyloid degeneration, or heart clots formed by incompetent muscular action of the heart, or thrombi resulting from sluggish circulation in distant small veins, or such as form in the small veins of the neck during the labored respiration of croup, were accused together with defective or paralyzed innervation. Buhl found also apoplexies in the spinal ganglia and in the gray substance of the spinal cord. As but few patients die of or during diphtheritic paralysis, the opportunities for making autopsies are comparatively rare. Still, before 1880, a number of observations were made which compare favorably with the results of modern researches. Buhl found considerable thickening of the spinal nerves at the junction of the posterior and anterior roots, with hemorrhages and diphtheritic exudation in the superficial connective tissue in these places. Oertel described in the sheath of the nerves in the cerebral and spinal meninges and in the gray substance of the cord voluminous nuclear infiltration, in one case extensive hemorrhages in the spinal meninges, with nuclear proliferation in the gray substance of the cord; Pierret found disseminated meningitis with perineuritis of the neighboring roots, characterized by infiltration of nuclei between the nerve fibrillæ; Charcot and Vulpian, degeneration of the palatine nerves and fatty disintegration of the palatine muscles; Dejerine, atrophy of the anterior roots secondary to a myelitic degeneration of the ganglia of the anterior horns; also in two cases liquefaction of myelin and loss of axis cylinders in intramuscular nerves.

The changes caused by diphtheria in the nervous system as described by one of the very latest writers on this much discussed subject (John Jenks Thomas, Boston City Hospital, 1898) are: 1. Marked parenchymatous degeneration of the peripheral nerves, sometimes accompanied by an interstitial process and by hyperæmia and hemorrhages; 2. Acute parenchymatous degeneration of the nerve fibres of the cord and brain; 3. No changes or but slight ones in the nerve cells; 4. Acute parenchymatous and interstitial changes in the muscles, especially in the heart muscle; 5. Occasional hyperæmia or inflammation or hemorrhages in the brain or cord, in rare cases severe enough to produce permanent troubles such as multiple sclerosis or hemiplegia. The writer adds that cardiac death probably takes place through the action of the toxin on the cardiac nerves. It is evident that the last twenty years have not added much, if anything, to the findings of the authors of decades ago.

To this may be added the results of some late experimentation. When B. Mouravieff injected diphtheria toxin into the subcutaneous tissue or into the peritoneum of guinea-pigs, acute or chronic symptoms made their appearance. Among the former were, in the ganglion cell of the anterior columns of the spinal cord, peripheral chromatolysis and extensive vacuolization, but no anæsthesia nor paralysis; among the latter were paralysis and more neuritis than ganglion-cell changes. Extensive peripheral neuritis was found only after five or six weeks.

Prognosis.

Epidemics differ. In some, mostly on account of the prevalence of mixed infections, the mortality is high, in others it is low. The last few years, not through the influence of antitoxin only, have been decidedly favorable, compared with many epidemics since 1858. The prognosis should always be considered uncertain, if only for the multiplicity and variety of possible complications.

Previous good health and vigor do not insure a good prognosis. Not infrequently a system accustomed to suffering, or perhaps immunized against known and unknown infections, though the general condition may seem unfavorable, will escape destruction, while a robust child will soon succumb. That is why the rich suffer at least as much as the poor. But when the infection is at an end, convalescence is speedier and more uninterrupted in the vigorous and well-to-do. Probably the external circumstances, better air, change of room, more thorough disinfection of rooms if there was a previous case, have a good deal to do with that result.

Very young age is unfavorable. The mortality is greatest below the first year of life, very large between the third and fourth, low after the eleventh or twelfth.

Children are more liable to suffer than adults. Very old people are almost immune; still I have seen a man of eighty-six years who had diphtheria and recovered. Very young infants are less subject, though, when they are taken, more endangered than children of from one to five years; still in 1880 I reported and quoted cases of diphtheria which occurred in the newly born. In regard to morbidity there appears to be no difference as to sex; mortality, however, has always been greater in boys. Among infants less than seven or eight months old the majority of cases occur below the third month.

In the child the mucous membrane of the mouth, throat, and nose is very soft and succulent; catarrhal and inflammatory changes with their epithelial alterations are frequent; the nasal cavities are narrow; the tonsils are comparatively large, indeed they are but rarely covered by the anterior pillars. Thus invasion and retention of bacilli are facilitated. The large size and number of the lymph vessels predispose to the absorption of toxins when formed. Children who are able to creep and to walk do not excel in cleanliness. Their fingers are equally well acquainted with their nares and their mouths as with the dust, dirt, and parasitic deposits on the floor of the room. Their lips are tentacles which examine and lick the crumbs on the floor, the toys in the dust, many of which are of wood or of felt and harborers of dust and microbes. Their faces and hands are seldom clean, and their handkerchiefs and towels are common property.

Such babies as cannot creep or walk are safer because they are mostly kept away from the floor and in their beds; they are not in intimate contact with their equals and possible sources of infection, but are nursed by adults. Their food is breast milk, or when artificial it is boiled. It was noticed a long time ago by Home and Canstatt that babies at the breast had but little disposition to "croup." Indeed such infants are not so subject to any of the contagious and infectious diseases as older children. Perhaps Schmid and Pflanz (*Wiener medizinische Wochenschrift*, No. 42, 1896) are correct in their opinion that woman's milk contains antitoxic materials; perhaps the immunizing alexins of the blood serum in the newly born are sufficiently powerful to guard against infections to a certain extent.

After the third month of life there is a copious secretion, slightly acid, from the mouths of infants. Both its quantity and its reaction militate against microbic invasion; that is why at that period diphtheria is less common than even in the first period of life; even a common angina is not frequent unless in cold seasons or after sudden changes of temperature, or when originating from a nasal catarrh which is of frequent occurrence.

The prognosis is favorable when the affected surface is not extensive and not in very intimate connection with the lymph circulation. That is why uncomplicated diphtheria of the tonsils and local cutaneous diphtheria, which latter is very amenable to treatment, are apt to be mild. Diphtheria of the lips and cheeks is of fair prognosis, partly because of the accessibility of these parts and partly because of the facility with which the natural secretions macerate and expel the membranes.

The thickness and solidity of the pseudomembrane are not bad in themselves. Even in the nose a massive membrane is not so dangerous as the thin, flocculent, putrid or sanguinolent discharge. Recoveries will occur though solid deposits fill both nares and have to be removed with probes and pincers. Fetid discharges need not be fatal, and bloody oozing which facilitates the direct absorption of toxins into the circulation may be successfully treated with irrigation, as taught by me these nearly forty years, when conscientiously made. Nor does the foul and sweetish odor of the breath justify a fatal prognosis, such as Roger, Oertel, and Kohts would pronounce. Everything depends on the accuracy and efficacy of the local disinfection. Still, nasal diphtheria when not interfered with is more fatal than even the laryngeal form.

Large swellings of the lymph bodies near the affected surface are ominous. They are not so frequent in uncomplicated bacillary diphtheria, as when the process is complicated with staphylococcic infection. Streptococci are still more dangerous—Variot's latest opinions as expressed in his "Diphthérie et Sérumthérapie," 1898, notwithstanding—on account of the early septicopyæmia which is apt to complicate the case. This mixed infection is mostly observed in diphtheria of the nares and nasopharynx. The frequently immense swelling of the lymph bodies near the angles of the lower jaw, together with periadenitis, is dangerous and will very seldom get well unless through the most careful disinfection of the original seat of the toxic infection. The outlook improves with the diminution in size of the lymph nodes and the accompanying periadenitis.

The degree of danger does not rise or fall with the temperature of a case. High fever attends sometimes a moderate catarrh of the pharynx, always a deep-seated inflammation of a tonsil—that is how an acute merely follicular "tonsillitis" may be distinguished from genuine diphtheria—and a general catarrhal laryngitis. A "pseudocroup" is therefore liable to set in with a high temperature; a laryngeal diphtheria is not attended with fever so long as it is local and uncomplicated. Still, an attack of diphtheria may set in with a high temperature—even convulsions are observed, partly occasioned by high temperature, partly by toxin—which will fall with the speedy elimination of the toxin. Low temperatures do not mean a mild character of the infection; on the contrary, a low temperature may attend cases of great gravity. Subnormal temperatures are very ominous; they accompany asthenia or collapse. If a moderate temperature be followed by a sudden rise, this may signify a sudden extension of the disease, but means usually the advent of a complication in a distant organ. A cold, clammy surface is a sign of bad prognostic import.

The pulse is very variable. It is seldom proportionate to the respiration, being usually more rapid. So long as it is of fair volume, and not too much out of proportion to the temperature of the body, the heart is strong enough; as soon as it becomes rapid and feeble, and moreover irregular, the prognosis becomes more grave. Under these circumstances the most active stimulation is demanded. In some instances the weak heart is not even able to multiply its beats, and the pulse becomes slow—a most dangerous symptom. If a frequent, compressible, and intermittent, or a slow and intermittent pulse be met with, together with a puffy, leaden, apathetic, and cachectic face, the prognosis is quite bad.

All of these symptoms mean a deterioration of the heart's action either by the direct effect of toxin on the nerves—a genuine cardiopulmonary paralysis—or by the presence of clots in the heart, of myocardial disintegration, or of a real ulcerous endocarditis. The latter is, however, more commonly the result of a streptococcal than of an uncomplicated bacillary invasion.

Affections of the blood-vessel walls leading to petechiæ or ecchymoses imply a bad, but not a fatal, prognosis.

The otitis media accompanying or depending upon diphtheria is prognostically not so bad as that which is observed in measles or scarlatina. Though deafness is not an infrequent outcome, operations are not so often demanded. Meningitis may occur in the contiguity of the tissue or by lymph communication; in either case it originates from the pharynx or from the nares, and often passes through the cribriform plate.

Pulmonary complications impair the prognosis. Broncho- or croupous pneumonias, many of which are caused by aspiration of more or less septic material, pulmonary hemorrhages, atelectasis caused by local impediments, and nervous incompetency are dangerous. The descent of membrane from the larynx or the spontaneous formation of membrane in fibrinous (not always diphtheritic) bronchitis is dangerous.

Paralysis of the laryngeal muscles and the presence of pseudomembranes in the larynx ("croup") are grave complications. There was a time when almost every patient was doomed, viz., before tracheotomy was introduced by von Roth, Krackowizer, and Voss into American practice. Even then the prejudice against the operation was great. When I performed it frequently after 1860 a famous surgeon was known to ask in all seriousness whether Dr. J. did not cut too many throats. Its results were impaired by improper procrastination and by the septic character of many of the epidemics. Improved antisepsis in tracheotomy, and O'Dwyer's intubation, which has almost entirely replaced the former operation, and its combination with the use of antitoxin have so much reduced the mortality of laryngeal diphtheria that old statistics have lost all except their historical value.

Albuminuria, which is often observed on the third or fourth day of the disease, is not by itself a grave symptom. Large quantities of albumin will sometimes disappear in a single day or in a few days—as they will occasionally do in other affections of the throat. So long as the amount of urine and the percentage of urea are normal or nearly so, the danger is trifling. But the presence of many epithelial cells, large casts, or blood, diminished or absent micturition, and perhaps even green or fecal vomiting, are grave symptoms. The intactness of the cerebral faculties during these attacks of nephritis should not be taken as a mitigating sign. In many cases and in many different epidemics I have seen consciousness preserved until within a few minutes before death. It is fortunate that actual nephritis is not so common in diphtheria as it is in scarlatina; altogether diphtheritic nephritis is not fatal to the same extent as the same disease when occurring in scarlatina.

The average case of diphtheritic paralysis permits of a fair prognosis. The patient generally gets well in from six to eight weeks under proper treatment. Extensive neuritis with fatty degeneration of the myocardium may paralyze the heart; paralysis of the pharynx and of the vestibule of the pharynx may lead to aspiration pneumonia; ciliary paralysis may remain permanent; that of the respiratory muscles may cause apnœa and death, and that of the sphincters of the anus and of the bladder, in the rare cases in which they have been observed, or of the spinal cord (tabes, hemiplegia) may last forever. That is why the prognosis in every case of diphtheria should be a guarded one until recovery is found to be complete.

TREATMENT.

Preventive Treatment.

Prevention is partly the business of the physician, but should be mostly that of the individual, or of the complex of individuals, viz., the town, state, or nation. A child sick with diphtheria must be isolated, though the case appear ever so mild, and if possible the well children should be sent out of the house. If that be impossible, let them remain outside, in the open air, as long as feasible, let them sleep in the most distant part of the dwelling with open bedroom windows during the night, and let their throats be examined every day. The watchful eye of an intelligent father or mother may discover deviations from the norm, so that the physician can be notified. Let the temperatures of the well children be taken once a day, in the rectum. The expenditure of a few minutes of a mother's time will be well repaid by the discovery of a slight anomaly, which may require the presence of the physician. Happily, there are many mothers who keep and value a self-registering thermometer as an important addition to their household articles. The attendant upon a case of diphtheria should not come in contact with the rest of the family, particularly the children, for the poison may be carried, although the carrier remains well or apparently well. The physician should see the well or suspected child before he visits the patient. Though not in protracted contact with their patients, medical men should use resaonable caution. Those visiting a diphtheria ward or a diphtheria patient should wear a clean linen cap or coat, or a rubber garment. E. M. Buckingham (*Boston Medical and Surgical Journal*, February 14th, 1895) disinfects the soles of his boots after leaving his ward, and soaks his hands and wrists in a solution (1:1,000) of corrosive sublimate which is allowed to dry. Unnecessary petting of the patient on the part of the well ought to be avoided, kissing shall be forbidden, the bedclothing and linen are to be changed often and disinfected, and the air must be kept cool and often changed.

During an epidemic of diphtheria, and in families stricken with diphtheria, the boiling of water and milk should be enforced.

The well or apparently well children of a family in which there is diphtheria must not go to school or to church. The former necessity is beginning to be recognized by the authorities and teachers, and also, in consequence of compulsion, by parents; but I have seen children after being excluded from the schools taken to church. Schools ought to be closed entirely when many cases have occurred. Even when the school children have not been extensively affected, but a diphtheria epidemic has commenced in earnest, it will be better to close the schools for a time. If that be not advisable, the teacher ought to be instructed to inspect throats, and directed to examine every child in the morning, and send home every one barely suspected. This is not superfluous even where a regular medical inspection has been introduced, as in New York City.

The Board of Health of the State of New Jersey has issued the following school regulations, which, if obeyed, cannot fail to have a good influence and should be adopted by similar authorities.

"I. Each day during the prevalence of infectious disease, after the school is dismissed, the janitor is to scrub with warm water, soap, and a stiff scrubbing-brush all parts of doors, casings, and other woodwork which can be touched by the hands of children. II. The floor should be in good repair and without open cracks or crevices. It should be sprinkled with clean water daily before being swept. III. Lead pencils (there should be no slates) should every day be immersed in a five-per-cent. solution (1:20) of carbolic acid and wiped dry. IV. Books which have been used by a pupil who is suffering from any one of the communicable diseases should be destroyed by fire or they may be treated by exposure to formaldehyde gas. V. During each vacation the walls and woodwork should be wetted with a solution of bichloride of mercury (1:1,000) and the windows should be kept open to admit great floods of sunlight and pure air. VI. Water coolers are unclean and unnecessary. They should not be allowed in school buildings. When practicable drinking fountains, consisting of a jet of water rising from the centre of a piece of marble, requiring no cups, should be supplied. VII. Individual seats and desks should be provided in every school. VIII. Light and airy cloakrooms should always be provided, and hooks should be so separated that the garments of different pupils will not come into contact."

In times of an epidemic, every public place, theatre, ballroom, dining-hall, tavern, should be treated like a hospital. Where there is a large conflux of people, there are certainly many who carry the disease with them. The spitting nuisance should be persistently suppressed. Disinfection at regular intervals should be enforced by the authorities. Public vehicles must be so treated. That they should be disinfected after a case of smallpox has been carried in them is deemed quite natural. Hardly a livery stable-keeper would be found who would not be anxious to destroy the possibility of infection in any of his coaches. He must learn that diphtheria is, or may be, as dangerous a passenger as variola. And what is valid in the case of a hack is more so in that of railroad cars, whether emigrant or Pullman. They ought to be thoroughly disinfected in times of an epidemic, at regular intervals, for the highroads of travel have always been those of epidemic disease, and railroad officers and their families have often been the first victims of the imported scourge. Can this be accomplished? Will not railroad companies resist a plan of regular disinfections because of its expensiveness? Will there not be an outcry against this despotic violation of the rights of the citizen, and the independence of the moneybag? Certainly. But that also happened when municipal authorities began to compel parents to keep their children at home when there were contagious diseases in the family, and when a smallpox patient was arrested because of endangering the passengers in a public vehicle. In such cases, it is not society that tyrannizes the individual; it is the individual that endangers society. And society begins at last, even in America, to believe in the rights of the commonwealth, as compared with the exclusive rights of the democratic enemy of all the rest. The establishment of state and national boards of health proves that the narrow-minded theories of the strict constructionists have not only disappeared from our politics, but also from the conscience and intellect of society.

As stated above, every case of diphtheria demands isolation, during the winter on the upper floor of the dwelling; the windows should be open as much as possible, the furniture of the sick-room reduced to the least possible quantity, the room changed if possible every few days, and the bedding renewed frequently.

To what extent the infecting substance may cling to surroundings is best shown by the cases of diphtheria springing up in premises which had not seen diphtheria for a long time, but had not been interfered with; and best, perhaps, by a series of observations of autoinfection. When a diphtheritic patient has been in a room for some time, the room, bedding, curtains, and carpets are infected; the child is getting better, has a new attack, may again improve, and is again stricken down. I have seen some of these children die; but also others who improved immediately after having been removed from that room or that house. If in any way possible, a child with diphtheria ought to change its room and bed every few days.

The sick in crowded houses and quarters ought to be transferred to a special hospital, which ought not to be too large. The Willard Parker Hospital of New York, with its seventy beds for scarlatina and diphtheria, established through the combined efforts of the medical profession,* is in that respect a praiseworthy example. The large amount of good it is doing would grow in geometrical progression if there were, as there ought to be in a large and ambitious metropolis, half a dozen institutions of the same class, not only for the poor, but for the well-to-do also, both towns-people and strangers. I have advocated, for dozens of years, the erection of a hospital for the accommodation of infectious diseases breaking out among the thousands of strangers staying in New York City at all times. As long as there is no place for them to go to, the cases of scarlatina, diphtheria, etc., are hidden in the boarding-houses and hotels, and are infecting the population at large. It is but a few years since a movement for the establishment of such an institution was begun; the hospital for scarlatina and diphtheria was finally established a year ago.

When diphtheria breaks out in a house, either private or tenement with no facility for isolation, and where there is no hospital in which to seek refuge, the well should be removed to a healthy place; in large cities, temporary homes ought to be provided for that purpose, to benefit the children of the poor. If the rich would but remember that their children will be affected through the many links between them and the poor (servants, messengers, schools, dresses brought home from the tailor or seamstress, or purchased in the stylish and expensive establishments which give out the work to tenement working-people and toilers in sweat shops), their very egotism would compel them to do in their own interest what the humanitarian instinct may not suggest to them.

Prevention can accomplish a great deal for the individual. Diphtheria will not, as a rule, attack a healthy integument, either cutis or mucous membrane. The best preventive is, therefore, to keep the mucous membrane in a healthy condition, as I have tried to practise and teach these forty years. Catarrh of the mouth, pharynx, and nose must be treated in time. Many a chronic nasal catarrh, with big lymph bodies round the neck, requires sometimes for its cure but two or three daily warm salt-water irrigations (1:130) of the nose, and besides, if the children be large enough to do so, gargling. The addition of one per cent. of alum or less will often be found useful. This treatment, however, must be continued for many months, and may require years. Still, there is no hardship in it, and no excuse for its omission. A. Caillé's many eloquent appeals have don emuch to popularize it. The nasal spray of a solution of nitrate of silver, 1:500–1,000, when there are erosions, will accelerate the cure. Its application should be repeated every day or every few days for some time.

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* See my presidential address before the Medical Society of the State of New York in the Transactions of 1882.

Krieger regarded the inhalation of dry (particularly furnace) air as the main predisposing cause of diphtheria on account of its deteriorating influence on epithelia. For a similar reason C. Brühl and E. Jahr[24] demand that both heating apparatuses and ventilators should be so arranged and so ample as to equalize the humidity in winter and summer, especially in bedrooms and in schools. The children should be hardened and strengthened by the use of cold water. Not only houses but whole districts may be treated on the same principles. Favorable climatological changes have often been produced by irrigation, the establishment of new channels, of water-courses, and intelligent forestry. But it would cost millions to save lives wholesale; and all these millions are required to destroy lives wholesale in haphazard wars. In accordance with the above-mentioned principles authors emphasize the necessity of keeping the mucous membranes moist, and of preventing fissures and disintegration of the epithelia. In the last two or three decades the latter advice has been insisted upon by all those who had waked up to the necessity of prevention. Among others C. G. Rothe (1884) advised besides hygienic measures the frequent use by all the inmates of a stricken house of a gargle consisting of carbolic acid, alcohol, tincture of iodine, glycerin, and water; also the use by all the children of a school of a solution of thymol (1:1,000) and cyanide of mercury for the very mildest affections. In connection with such advice one remark will always be in order, viz., that medicinal gargles and irrigations should not be as unpalatable and malodorous as they can possibly be made; children should not be made to look upon preventive measures as a punishment.

It was not always good-will and intelligence or knowledge that dictated either reasoning or recommendations. There is J. Renan, for instance, who in his "Diphthérie," Paris, 1889, recommended the free use, among preventives, of sulphurous acid and turpentine. Altogether the literature of diphtheria is not free even from religious and political bias. According to Renan's monarchistic prejudices the inferiority of preventive practice in (republican) France is due to the changeability of its government. According to that theory Turkey and Russia would excel in preventive medicine, for—barring occasional assassinations—their governments are stable enough.

For its salutary effect on the mucous membrane of the mouth, chlorate of potassium or of sodium, which is still claimed by some to be a specific in diphtheria, or almost so, is counted by me among the preventive remedies. If it be anything more, it is an adjuvant only. It exhibits its best effects in the catarrhal and ulcerous condition of the oral cavity. In diphtheria it preserves the mucous membrane in a healthy condition or restores it to health. Thus it prevents the diphtheritic process from spreading.

Diphtheria is seldom observed on healthy or apparently healthy tissues. The pseudomembrane is mostly surrounded by a sore, hyperæmic, œdematous mucous membrane, to which it will then extend. Indeed, this hyperæmia precedes the appearance of the diphtheritic exudation in almost every case. The exceptions to this rule are formed by those cases in which the virus may take root in the interstices, pointed out by Stoehr, between the normal tonsillar epithelia. Indeed, many cases of throat disease occurring during the prevalence of an epidemic of diphtheria are but cases of pharyngitis which develop only under favorable circumstances into diphtheria. These throat diseases are so very frequent during the reign of an epidemic that in my first paper on diphtheria, while reporting two hundred cases of genuine diphtheria, I mentioned besides one hundred and eighty-five of pharyngitis without a visible membrane.

These cases of pharyngitis, and those of stomatitis and pharyngitis which accompany the presence of membranes, are benefited by the local and general effect of potassic chlorate. When the surrounding parts are healthy or return to health, the pseudomembrane remains circumscribed. The generally benign character of purely tonsillar diphtheria, which is apt to run its full course in from four to six days, has in this manner contributed to secure to chlorate of potassium the undeserved reputation of being a remedy, *the* remedy, in diphtheria. The dose of the salt must not be larger, in twenty-four hours, than gr. xv. (1 gm.) for an infant a year old, not over gr. xx. or xxx. (1.5–2 gm.) for a child from three to five years. An adult should not take more than ʒ iss. (6 gm.) daily. These amounts must not be given in a few large doses, but in frequent doses and at short intervals. A solution of 1 part in 60 may be given in doses of a teaspoonful every hour or half a teaspoonful every half-hour in the case of a baby one or two years old.

It is not too late yet to raise a warning voice against the use of larger doses. Simple truths in practical medicine do more than merely bear repetition—they require it. For though the cases of actual chlorate-of-potassium poisoning are no longer isolated, and ought to be generally known, fatal accidents are still occurring even in the practice of physicians. When I experimented on myself with half-ounce doses, forty years ago, the results were some gastric and intense renal irritation. The same were experienced by Fountain, of Davenport, Iowa, whose death from an ounce (30 gm.) of the salt has been impressively described in Alfred Stillé's "Materia Medica," from which I have quoted in my "Treatise on Diphtheria." His death from chlorate of potassium induced me to warn against large doses in my lectures as early as 1860. In my contribution to Gerhardt's "Handbuch der Kinderkrankheiten," Vol. II., 1877, I spoke of a series of cases known to me personally. In a paper read before the Medical Society of the State of New York (*Medical Record*, March 15th, 1879) I treated of the subject monographically, and alluded to the dangers attending the promiscuous use of the drug, which had even then descended into the ranks of domestic remedies; and finally, in my "Treatise on Diphtheria," I collected all my cases and the few then recorded by others. Since that time numerous instances have been reported. Death probably occurs from methæmoglobinuria (as shown by Marchand, of Halle, in 1879), produced by the presence of the poison in the blood, and by consecutive nephritis.

The conscientious use of salt water as a preventive measure will prove more successful—when combined with the daily cold-water bath or ablution—than all the offensive smells and tastes which have been recommended.

Large tonsils should be resected and adenoid growths removed while there is no diphtheria; for during an epidemic every wound in the mouth is liable to become diphtheritic, and such operations ought to be postponed, if feasible. The scooping out of the tonsils, for whatever cause, I have given up since I became better acquainted with the use, under cocaine, of the galvanocautery. From one to four applications to each side are usually sufficient for every case of enlarged tonsils or chronic lacunar or deep-seated follicular amygdalitis ("tonsillitis"). It is advisable to cauterize but one side at a time, in order to avoid inconvenience in swallowing afterwards, and to burn the surface inward. Cauterization of the centre of the tonsils may result in swelling, pain, and suppuration, unless the cautery is carried entirely to the surface; that means, the scurf must be on, or extend to, the surface, and not remain inside the tissue. Another precaution is to apply the burner cold, press it on, and then heat. The actual cautery is, however, not always required; a strong hook, without or with Gleitsmann's cutting edge, bent to a convenient angle, introduced into a follicular fistula, and torn through the superjacent tissue, will also cause cicatrization and a cure.

Nasal catarrh and proliferation of the mucous and submucous tissues may require appropriate treatment with the electrocautery in many chronic cases, but the cases which demand it are less frequent than those in which the tonsils need correction.

The presence of lymph-node swellings round the neck should not be tolerated. They and the oral and nasal mucous membranes affect each other mutually. Most of them could be prevented if every eczema of the head and face, every stomatitis and rhinitis resulting from uncleanliness, injury, or infection, were relieved at once. Painstaking care of that kind would prevent many a case of diphtheria, glandular suppuration, deformity, or pulmonary consumption.

Prevention of diphtheria by immunizing doses of *antitoxin* appears to be possible, but the effect does not last beyond a few weeks.

Slawyk's report, published in the *Deutsche Medicinische Wochenschrift*, No. 6, 1898, is very interesting. In Heubner's division of the Charité Hospital of Berlin relapses of endemic infections were quite common in spite of careful preventive measures until immunization by antitoxin was resorted to. The doses, of two hundred units contained in 8 c.c. each, were repeated every three weeks. In this way the place remained free of diphtheria. As a matter of experiment immunization was discontinued on October 1st, 1897. Three cases of diphtheria, one of which terminated fatally, occurred in the first part of November. The preventive injections were then made again, and during the following two and a half months, up to the time the report was published, no new case had been observed. Neither early age nor any complicating disease appeared to furnish a contraindication to the injections.

Similar results have been obtained in New York and elsewhere. The duration of the immunity so obtained is, however, limited. It has frequently been observed that a dose of from two to four hundred units of antitoxin, when given for immunizing purposes, appeared to be successful, until the child was taken with diphtheria thirty or forty days after the injection.

In connection with the preventive measures detailed above, I now add, though they be in part a repetition of what has been said, the regulations of the New York Health Department which have been in force for some time. They are clear, concise, and to the point.

"If possible, one attendant should take the entire care of the sick person, and no one else beside the physician should be allowed to enter the sick-room. The attendant should have no communication with the rest of the family. The members of the family should not receive or make visits during the illness.

"The discharges from the nose and mouth must be received on handkerchiefs or cloths, which should be at once immersed in a carbolic solution (made by dissolving six ounces of pure carbolic acid in one gallon of hot water, which may be diluted with an equal quantity of water). All handkerchiefs, cloths, towels, napkins, bed linen, personal clothing, night clothes, etc., that have come in contact in any way with the sick person, after use should be immediately immersed without removal from the room in the above solution. These should be soaked for two or three hours, and then boiled in water or soapsuds for one hour.

"In diphtheria and scarlet fever, great care should be taken in making applications to the throat or nose, that the discharges from them in the act of coughing are not thrown into the face or on the clothing of the person making the applications, as in this way the disease is likely to be caught.

"The hands of the attendant should always be thoroughly disinfected by washing in the carbolic solution, and then in soapsuds, after making applications to the throat or nose, and before eating.

"Surfaces of any kind soiled by the discharges should be immediately flooded with the carbolic solution.

"Plates, cups, glasses, knives, forks, spoons, etc., used by the sick person for eating and drinking must be kept for his especial use, and under no circumstances removed from the room or mixed with similar utensils used by others, but must be washed in the room in the carbolic solution and then in hot soapsuds. After use the soapsuds should be thrown into the water-closet and the vessel which contained it should be washed in the carbolic solution.

"The room occupied by the sick person should be thoroughly aired several times daily, and swept frequently, after scattering wet newspapers, sawdust, or tea leaves on the floor to prevent the dust from rising. After sweeping, the dust upon the woodwork and furniture should be removed with damp cloths. The sweepings should be burned, and the cloths soaked in the carbolic solution. In cold weather, the sick person should be protected from draughts of air by a sheet or blanket thrown over his head while the room is being aired.

"When the contagious nature of the disease is recognized within a short time after the beginning of the illness, after the approval of the Health Department inspector, it is advised that all articles of furniture not necessary for immediate use in the care of the sick person, especially upholstered furniture, carpets, and curtains, should be removed from the sick-room.

"When the patient has recovered from any one of these diseases the entire body should be bathed and the hair washed with hot soapsuds and the patient should be dressed in clean clothes (which have not been in the room during the sickness) and removed from the room. Then the Health Department should be immediately notified, and disinfectors will be sent to disinfect the room, bedding, clothing, etc., and under no conditions should it be again entered or occupied until it has been thoroughly disinfected. Nothing used in the room during the sickness should be removed until this has been done.

"The attendant, and any one who has assisted in caring for the sick person, should also take a bath, wash the hair, and put on clean clothes, before mingling with the family or other people after the recovery of the patient. The clothes worn in the sick-room should be left there, to be disinfected with the room and its contents by the Health Department."

Among the disinfectants employed to advantage in dwellings formalin has of late taken a high rank. A spray of a two-per-cent. solution has been found available. From 60 to 70 c.c. of dissolved concentrated formalin is believed to be sufficient for the space of one cubic metre (thirty cubic feet). One gram of formaldehyde evaporated from Schering's lamp or other apparatus renders the same service; or the substance may be allowed to evaporate gradually. Meanwhile the eyes should be protected by glasses, the nose by a mask, the hands by vaseline. Still, if Symansky be correct (*Zeitschrift für Hygiene*, etc., xxviii., 1898, p. 237), even formalin leaves much to be desired. He claims, while mentioning in its favor that it does not injure clothing and furniture, with the exception of changing red aniline dyes into purple, that its best effect is obtained at high temperatures and in dry atmospheres, and that it has but little penetration and destroys no spores, and for that reason yields no absolutely safe results.

Local Treatment.

The local remedies employed have been used for the purpose of either directly destroying the pseudomembrane, such as nitrate of silver, carbolic acid, the actual cautery; or to dissolve them, such as the alkaline carbonates, the chlorides, steam, papayotin; or to act as astringents, such as limewater and the chloride and subsulphate of iron; or to disinfect, such as the potassic chlorate, chloral hydrate, turpentine, carbolic acid, mercury, sulphur, bromine, iodine, iodoform, chlorine water, and peroxide of hydrogen. The methods of application have been either direct local administration by the attendant, or washes and gargles, sprays, injections, or inhalations.

The local treatment of the mouth and throat has two indications: first, to maintain or restore a healthy condition of the mucous membrane of the cavities; second, to influence the diseased surface. Gargles in any shape will reach the oral cavity only. They never touch anything beyond the anterior pillars of the soft palate, and seldom more than a small part of the tonsil. The gargles with potassic chlorate, or with the sodic benzoate or biborate have only a preventive, not a curative, effect; still, they ought not to be neglected when the children are old enough to use them. Mild solutions of the above salts may also be introduced into the mouth of babies from time to time by means of a brush or a pipette. Local applications to the throat, even where they are possible, ought not to be made with powders. They are apt to nauseate and produce vomiting by their mere contact. Even powders for internal administration require careful mixing with water, for they are liable to irritate the throat; thus, the direct application of calomel, of the oxide of mercury, or of sulphur ought to be avoided. Applications of substances with bad taste or those that give pain must not be made, because the struggling and consecutive exhaustion of the patient will do more harm than the remedy will do good. That is so with a number of substances, particularly with the chloral hydrate, and even with the chloride of sodium which has been recommended, like a hundred other things, as a local application to the pseudomembrane of the tonsil.

In diphtheria the danger arises first from suffocation. That can be easily recognized, and the indications for the treatment by mechanical means—that is, intubation or tracheotomy—are readily found. These are the cases in which repeated fumigations with gr. vii.–xv. (0.5–1 gm.) of calomel, under a tent or in a small room, are used to advantage. Steam will also answer well under the same circumstances.

When the diphtheritic pseudomembrane is within reach, it should be either destroyed or disinfected. For that purpose one or two drops of a fifty-per-cent. solution of carbolic acid in glycerin may be applied once (not more than twice) a day, or of the tincture of iodine, or of a solution of 1 part of the bichloride of mercury in 100 or 500 parts of water, several times a day. It is in these cases that chlorine water has been injected through the surface into the upper layers of the tonsils. But we should never forget that only a small part of the pharynx is accessible to such treatment, and that it is only one class of patients that can be subjected to it. In order to be effective, the application must be thorough. None but adults or large children, and of them only a small number, will submit to opening their mouths and to the applications. It is that very class of patients who can be induced to gargle with some little, though very little, success. Smaller children will object, will defend themselves, will struggle. It takes many an anxious moment to force open the mouth; meanwhile, the patient is struggling, perspiring, screaming, and exhausting his strength. One may succeed in forcing open the jaws, then there begins the practice of making applications, of swabbing, of scratching off the pseudomembrane, of cauterizing, of burning. The struggling child will prevent the limitation of the application to the diseased surface. One cannot help injuring the neighboring epithelium, and thus the morbid process will spread. Instead of doing good, we have done harm; for, indeed, no local application can do so much good as the struggles of the frightened children do mischief. I have seen them die while defending themselves against the attempted violence, leaving doctor and nurse victorious and alive on the battlefield. It is incredible, but it is true, that more than one have recommended using the electrŏcautery or the thermocautery on the throat of the baby, after forcing the mouth open! It is almost incredible, for the offenders cannot have been ignorant of the fact that what they can reach with their instruments is but very little besides the tonsil, and they might have known that it is just the tonsils that are least apt to favor the admission of sepsis into the circulation.

There is an easy way of using disinfectants on the throat and mouth, viz., to give medicines which are at the same time disinfectants, digestible, and easy to take; to give them in small doses but frequently; to see that when they have been given, no water or milk is taken immediately afterwards, so as not to wash them off from the mouth and throat. Such medicines are mild dilutions of the tincture of chloride of iron, or lime water, or solutions of boric acid, or of bichloride of mercury, or of benzoate of sodium, most of which will act both by their constitutional and their local effect.

Diphtheria is most dangerous when located in the nose and nasopharynx. The changes taking place in the nares may be an extensive catarrh, besides the diphtheritic deposits. The diphtheritic membranes are sometimes very thick, and contain a great deal of fibrin. Sometimes they are so thick as to clog the nares and prevent respiration. Underneath them copious absorption of toxins may take place. In most cases, however, the diphtheritic membranes are not so thick. Some of them macerate very readily, and the toxin is very speedily absorbed through the exceedingly copious lymph ducts, and sepsis is the result. In some cases of diphtheria, however, the membranes can hardly be seen. The discharge from the nose is liquid and acrid, contains small flakes and some blood. These are the cases in which the toxin is absorbed directly into the circulation. All of these forms may lead to necrosis and gangrene of the tissue, and produce a very peculiar, sweetish, nasty odor. Thus, the inhaled air is poisoned, and, being carried down into the lungs, acts as an additional peril. The most dangerous locality is the posterior nares, with their direct communications with the lymph bodies below the angle of the lower jaw. The pseudomembranes, the lymph ducts, and lymph bodies, swarm with bacilli and toxin, with streptococci, with staphylococci, and lead to immense tumefaction between the ears and clavicles, to the formation of multiple small abscesses, to hemorrhages, to sepsis. All of these forms of nasal diphtheria require immediate, persistent, and efficient local treatment, for it is safe to say that every case of genuine or mixed nasal diphtheria has a tendency to terminate fatally.

The local treatment consists in cleansing and disinfecting. In most cases these two are identical, for if we simply succeed in washing out the macerating material, that proves sufficient. In order, however, to have that effect, the washing and disinfecting must be done often—every half-hour, every hour, every two hours, day and night. In the bad cases, in which the nares are clogged with pseudomembrane, the cleansing and disinfecting are to be preceded by forcing a passage through the nares with a probe covered with wadding and dipped in carbolic acid. Particularly is this indication urgent when there is sopor, which owes its origin partly to the difficulty of respiration and carbonic-acid poisoning and partly to the septic condition. The methods of local treatment, besides the one just described, are the (not always successful) applications of ointments within the nose by means of the brush or wadded probe, or the use of the spray or syringe or irrigator, or the use of a spoon or a nasal cup or a feeding-cup, through which liquids are poured into the nares. The indispensability of these nasal administrations cannot be urged too positively. Park thinks that "when the strength is good and the nostrils and throat are full of discharge and membrane, it is well to insist on cleansing by irrigation; when, however, the child is much prostrated, and struggles against it, irrigation may have to be omitted" ("An American System of the Practice of Medicine," i., p. 684). I believe, however, that in nasal diphtheria local treatment is the vital indication.

In making local applications it is important that the whole surface should be touched; therefore neither ointments nor instillations from a medicine-dropper are available in the average cases in which the whole nasopharynx is the seat of the affection; nor as a rule will the atomizer convey a sufficient amount of liquid into the cavities to be of much use. A spoon or a small feeding-cup, or better one of the nasal cups made for the purpose the nozzle of which is narrow enough to enter the nose, will do fairly well, and will allow the introduction of liquids into the nares in small or large amounts, all of which will enter the throat, be either swallowed or flow out of the other nostril or out of the mouth. The irrigator (fountain syringe) is liable, by undue pressure, which cannot always be well measured, to injure the ear. It is true that this cannot take place very readily so long as the whole nasopharynx is covered with pseudomembrane, but this will not always remain, and then there is a possibility of the injection, when forced in, entering the middle ear. This will take place the more readily the younger the infant, because the pharyngeal orifice of the Eustachian tube is relatively larger and more funnel-like in the very young than in those of more advanced age. On the other hand, this configuration of the Eustachian tubes favors the escape of fluids from the middle ear; that is why otitis media in the very young is often painless. I generally prefer a small glass syringe with a conical nozzle of soft rubber. It will close up the nostril, the pressure can always be measured and modified (it should be very gentle), and it is effective. The injections must be made with the patient in the recumbent or semirecumbent position. On no condition, however, must a child with diphtheria be taken out of bed for the purpose of having the nares washed and disinfected. I know of many cases in which the patient died simply from being repeatedly taken up. The injection or irrigation is best made by a person who sits on the edge of the bed behind the patient, and raising his head gently supports it with his chest. A towel should quickly be thrown over the chest of the patient, and another attendant should secure the patient's hands. All preparations should be made out of sight. Slow irrigation should always be preferred to injection when there is some bleeding after every application.

The fluids to be used may be quite simple, but should always be warm. In many cases a solution of table salt in water (7 : 1,000), or boracic acid (2 or 4 : 100), or lime water will answer all purposes. The latter is particularly indicated when there is a thin, acrid, slightly fetid discharge. A more efficacious disinfectant than all of those mentioned is the bichloride of mercury, 1 part mixed with 10 parts of chloride of sodium or chloride of ammonium in from 2,000 to 10,000 parts of water. It may be used freely.

If moderate quantities of a mild solution of bichloride of mercury be swallowed while being injected, no harm is done. Where there is a fetid odor, the nares ought to be deodorized frequently by carbolic acid or creolin or permanganate of potassium.

Carbolic acid may be used in solutions of from 1 to 10 : 1,000 parts of water, but it should not be forgotten that there is some danger in swallowing it, because of the nephritis to which it may give rise. For the same purpose of deodorizing, creolin may be used in one-per-cent. solutions. Löffler's solution of alcohol 60, toluol 36, and tincture of iron sesquichloride 4 parts, does not act better than others, has a bad taste, is objected to very strongly, and gives rise to exhausting struggles. Permanganate of potassium in solution (1 : 250) may be applied once or twice a day to the fetid nares with a probe wrapped in absorbent cotton, or may be used for spraying, for jection, or for irrigation in a solution of 1 : 2,000–4,000 many times a day. Peroxide of hydrogen is a powerful disinfectant; some of its eulogizers condemn such preparations as are acid, others those which are not acid. Solutions which are not very thin will coagulate the soluble albumin of the surface tissue with which they come in contact; form membranous deposits which are frequently mistaken for diphtheritic pseudomembranes; give rise, when the membranous artefacts will have been thrown off, to local sores, which may, and very often do, furnish a resting-place to new microbic invasions. This should be taken into consideration and is true, though one of the manufacturers of this substance once tried to increase the vigor of the advertisement of his wares by coupling with it his conviction of my ignorance on the subject.

For the purpose of *dissolving membranes*, papayotin (not the proprietary medicine sold under a similar name) has been used in five-per-cent. solutions, as a spray, by injection, or as a direct application by means of a sponge or brush. Many years ago I employed it in greater concentration to dissolve the diphtheritic membranes of the trachea below the tracheotomy tube. Its application in powder does not answer well. For the same purpose trypsin has been employed in five-per-cent. solutions, mixed with bicarbonate of sodium.

The *cervical lymphadenitis*, of which I have spoken as the result of nasal diphtheria, must be treated persistently and effectively. This treatment may be preventive and curative. The preventive treatment consists in the nasal injections described. The rapidity with which large swellings diminish when irrigations are made frequently and conscientiously is often surprising. When large tumefaction has taken place, tincture of iodine has been applied externally; in that way it is useless. Mercurial ointments and oleates have been applied; they also are useless, either as actual remedies or as a means of massage. An ointment of potassic iodide and adeps lanæ hydrosus (1 : 6–8) is more readily absorbed and less irritating. Ice externally is rational, but it is useless so long as the infection is not stopped. I have in a number of instances injected iodoform, in ether, into the swelled mass, but it is too painful and too inefficacious, and does not pay for the agitation, anguish, and exhaustion of the unfortunate child. So, indeed, there is no remedy, besides the preventive measures, except in occasional long and deep incisions into the immense mass. We should not wait for fluctuation or even semifluctuation to become apparent. A great deal of the swelling is inside the fascia. Abscesses, when they form, are seldom large. The contents consist more of necrotic tissue, which ought to be laid open as soon as possible and disinfected. The incision must be a long one—in many cases from ear to clavicle. The disinfection of the wound may be obtained by applications of subnitrate of bismuth or tincture of iodine, and by iodoform or other antiseptic gauze. No carbolic acid should be used for disinfection, because of its tendency to give rise to hemorrhages. When a hemorrhage takes place, it will usually stop under pressure with antiseptic gauze; but sometimes, when a large blood-vessel has been eroded, it is very copious. In such cases the actual cautery, acupressure, or sometimes the ligature of blood-vessels has to be resorted to. Chloride of iron and subsulphate of iron must never be used on such necrotic surfaces. They give rise to a thick coagulated scab under which septic absorption is apt to take place.

Sanguinolent discharges from the nostrils may usually be arrested by the conscientious application of cleansing and disinfecting solutions (in most cases gentle irrigation works best). But the subsulphate or perchloride of iron should generally not be employed for the reason above given. The application of a solution of antipyrin (1 : 10, sometimes 1 : 3) by means of a swab or a spray will generally prove satisfactory in hemorrhages. In urgent cases a tampon saturated in a solution of antipyrin is required; its styptic property is enhanced by the addition of a small amount of tannic acid.

Moderate hemorrhages from the throat should be treated in a similar way, and by ice-bags properly applied. Unless they be parenchymatous their locality should be inquired into for the purpose of the localization of a styptic—antipyrin, or the actual cautery. If there be an erosion of a large vessel, such as the carotid artery in a case reported by me in the Transactions of the Association of American Physicians (1898), nothing short of the ligation of the vessel is appropriate. If it be the jugular vein which is ruptured, either ligation or compression should be resorted to.

Local treatment has lost its credit with some who believe that antitoxin alone should be relied on in all cases and for all indications. That is a grave mistake, which will again be referred to below.

For the purpose of softening and macerating pseudomembranes steam has been extensively utilized. Its inhalation is useful in cases of catarrh of the mucous membranes, and in many inflammatory and diphtheritic affections. On mucous membranes it will increase the secretion and liquefy it, and thus aid in the throwing off of the pseudomembranes. Its action is the more pronounced the greater the amount of muciparous follicles under or alongside a cylindrical or fimbriated epithelium. Thus it is that tracheobronchial diphtheria and the non-bacillary forms of fibrinous bronchitis are greatly benefited by it. Children affected with them I have kept in small bathrooms for days, turning on the hot water, and obliging the patient constantly to breathe the hot vapor. In several such cases I have seen recovery with that treatment. Atomized cold water will never yield the same result; nor have I seen the patented inhalers do much good. Still, where the surface epithelium is pavement rather than cylindrical, and where but few muciparous follicles are present, and when the pseudomembrane is rather immerged in, and firmly coherent with, the surface—for instance, on the tonsils—the steam treatment is less appropriate. On the contrary, moist heat is liable in such cases to favor the extension of the process by softening the hitherto healthy mucous membrane. Thus it takes all the tact of the practitioner to select the proper cases for the administration of steam, not to speak of the judgment which is required to determine to what extent the exclusion of air (oxygen) from the steam-moistened room or tent is permissible.

Steam may be properly mixed with medicinal vapors. In the room of the patient water is kept constantly boiling over the fireplace, provided the steam is prevented from escaping directly into the chimney, on a stove (the modern "self-feeders" are insufficient for that purpose and are abominations for every reason), over an alcohol lamp, if we cannot do better, but not on gas, if possible to avoid it, because of the large amount of oxygen which it consumes. Every hour a tablespoonful of oil of turpentine, or of eucalyptus, and perhaps also a teaspoonful of carbolic acid, is poured on the water and evaporated with it. The air of the room is filled with steam and vapors, and thus the contact with the sore surfaces and the respiratory tract is obtained with absolute certainty.

The secretion of the mucous membranes is sometimes quite abundant under the influence of steam, but is still more, like that of the external integuments, increased by the introduction of water into the circulation. Therefore, drinking of large quantities of water or of water mixed with an alcoholic stimulant should be encouraged. Over a thoroughly moistened mucous membrane the pseudomembrane is more easily made to float and to macerate.

To evolve large volumes of steam the slaking of lime has been resorted to. It is both an old and an effective procedure. Not only is the object in view accomplished by it, but it is the best means of bringing lime into contact with the morbid surface. In a room in which lime has been slaked, everything is covered with it. Thus this method of profiting by the local effect of lime is decidedly preferable to the almost nugatory effect of lime water sprayed into the throat.

In connection with these measures, taken for influencing the mucous secretions and exudations of the mucous membranes, I may here refer to some internal medication resorted to with the same object in view. It was to fulfil the same indication of softening the pseudomembrane, by increasing the secretion of the mucous membranes, that pilocarpine or jaborandi was highly recommended (Guttmann) as a panacea in all forms of diphtheria. There is no doubt that the secretion of the mucous membranes is vastly increased by the internal administration, or by repeated subcutaneous injections of the muriate or nitrate of pilocarpine, but the heart is enfeebled by its use. I have seen but few cases in which I could continue the treatment for a sufficient time. In many I had to stop it because after some days of persistent administration I feared for the safety of the patients. Therefore, as early as 1880, at the meeting in that year of the American Medical Association at Richmond, I felt obliged to warn against its indiscriminate use in diphtheria. Thus it has shared the fate of all the hundreds of remedies and methods which have been declared to be infallible and have been found wanting.

The diphtheritic *conjunctiva* should be irrigated frequently, every half-hour or every hour, with a mild antiseptic solution (boracic acid 1–4 : 100). These irrigations are quite often difficult to make because of the massive infiltration of the tissues. To counteract this and its pressure on the eyeball I saw, thirty years ago, a deep horizontal incision made through the external angle. In some cases the pressure was relieved in spite of the extension of the diphtheria along the wound. Ice applications to the eye are always indicated, particularly at first. If bags will not be tolerated, cloths large enough to cover the eye should be placed on a lump of ice and applied fresh, without previous wringing, every two minutes. These ice applications should, however, be watched. They are liable to increase the anæmia caused by the infiltration of the tissues and give rise to necrosis. Such occurrences should be met by warm applications, which may increase the tendency to maceration. Abscesses in the lower part of the cornea should not be opened. Accompanying eczema or erythema of the cheeks should be treated with an iodoform-vaseline ointment (1 : 6–10), and cellulitis of the surrounding tissue of the cheek according to the common principles of antiseptic surgery.

Ammann treated six serious cases of diphtheria of the eye with repeated injections of antitoxin, which were not successful. It appears its effect is doubtful when the cornea is affected, and mainly, as it happened in his cases, when diphtheritic conjunctivitis and keratitis were complicated with the presence of cocci.

General Treatment.

The *dietetic treatment* of a case of diphtheria, either simple and uncomplicated, or mixed, or septic, should be guided by circumstances and general principles. Solid food is rarely relished and generally refused, though there be but little pain in swallowing. A child may be permitted to go without food for the first day or longer. But the tendency to leucocytosis, hydræmia, and toxic exhaustion demands measures for the preservation and restoration of strength. Milk in different forms, with and without farinaceous admixtures, broths and beef juice, eggs in acceptable form, and alcoholic stimulants at an early time should be insisted upon. It is only necessary to urge the necessity, while trying to remove the disease, of preserving the patient.

The *medicinal treatment* of an average case of *pharyngeal diphtheria* can be made to combine the indications of both internal and local administration. For forty years I have employed the tincture of the chloride of iron. It is an astringent and antiseptic. Its contact with the diseased surface is as important as is its general effect; therefore it should be given frequently, in hourly or half-hourly doses, even every twenty or fifteen minutes. An infant of a year may take 3 or 4 c.c. (ʒ i.) a day, a child of three or five years 8 or 12 c.c. (ʒ ij. or iij.). It is mixed with water so as to make the dose half a teaspoonful or a teaspoonful; a drachm or two drachms (4 or 8 c.c.) with a small quantity of chlorate of potassium (see above), in four ounces (120 c.c.) allows half a teaspoonful every twenty minutes. No water must be drunk after the medicine. As a rule, it is well tolerated. There are some, however, who will not bear it well. Vomiting or diarrhœa is a contraindication to perseverance in its use, for nothing must be allowed to occur which reduces strength. A good adjuvant is glycerin, and better than syrups. From ten to fifteen per cent. of the mixture may consist of it. Now and then, but rarely, it is not at all tolerated. When diarrhœa sets in glycerin should be discontinued. Still, these cases are rare; indeed, the stomach bears glycerin very much better than the rectum.

I have seen so many bad cases recover under the administration of chloride of iron, when treated after the method detailed above, that I cannot rescind former expressions of my belief in its value. Still, I have often been so situated that I had to give it up in peculiar cases. They were those in which the main symptoms were of so intense a sepsis that the iron and other rational methods of treatment were not powerful enough to prevent the rapid progress of the disease. Children with nasopharyngeal diphtheria, large glandular swelling, feeble heart, and frequent pulse, thorough sepsis, and irritable stomach besides, those in whom large doses only of stimulants, general and cardiac, may possibly bring any relief, are better off without the iron. When the circumstances are such as to leave the choice between iron and alcohol, it is best to omit the iron and rely on alcoholic stimulants mostly. The quantities required are so large that the absorbent powers of the digestive tract are no longer sufficient for both.

Nor is iron sufficient or safe in those cases which are preeminently laryngeal. To rely on iron in membranous croup means both waste and danger.

When pharyngeal diphtheria has reached the *larynx* in its descent, or when bronchial diphtheria in its ascent has resulted in sudden laryngeal stenosis, the above antidiphtheritic treatment avails but little. That neither general nor local depletion has any effect, except that of hopelessly reducing the patient's strength, has long been recognized; also that vesicatories add new diphtheritic exudations on the denuded surfaces to those already on the mucous membranes. Emetics are of no use unless a peculiar flapping sound betrays the presence of half-detached membrane in the air passage. In such a case they are apt to save life. Massage of the larynx has been recommended by Bela Weiss. I cannot say that the few cases in which I advised the procedure were successful; it may be that the constant repetition of the advice to use mercurial or other ointments over the larynx is based on the observation of an occasional good effect of the friction ("massage") attending their employment. Locally, lactic acid, in more or less saturated solution, has been eulogized as a solvent of the membranes in the larynx, when often applied either by brush or spray. Most of the cases in which I have seen it used were not successful; but an untoward result in these cases is, unfortunately, not exceptional. I have seen, or believe I have seen, papayotin dissolve membrane when applied in a mixture of one part in two parts each of glycerin and water. Particularly would that occur in pharyngeal diphtheria slowly descending. Lime water is still used as a spray and has its admirers. Lime slaked in a small room, or under a tent, is decidedly more effective, for during that process a large quantity of lime is carried up and inhaled; at the same time the softening and solvent effect of the steam is obtained, but the latter is not always so beneficent as it appears. In many the application externally of cold water or ice-bags to the neck is vastly preferable. But in most cases of anæmic and highly nervous children the latter are not tolerated. Constant inhalations of turpentine or carbolic acid from a kettle of boiling water have impressed me as beneficial in a large number of cases. Inhalations, in a small room or under a tent, of calomel, which is sublimated in doses of gr. viij. or x. (0.5 gm.), every hour or at longer intervals, are certainly effective.

The patient remains in bed as much as possible, and may continue such expectorants as he perhaps took for previous catarrhal symptoms; he may also take diaphoretics and warm beverages; an occasional opiate to excite diaphoresis and to procure some rest. The continued use of chlorate of potassium, when the invasion of the larynx is complete, is rather superfluous. Antipyretics are out of the question unless there is a very high temperature depending on a complication (general diphtheria, pulmonary inflammations). Pilocarpine injures by debilitating the patient; the cases which are really benefited by it are excessively rare. Mercurials have resulted in more actual recoveries than has any other internal treatment. The cyanide and iodide have been recommended. For nearly twenty years I have employed the bichloride in doses of 1 mgm. (gr. $\frac{1}{60}$) or more once every hour. The smallest babies take one-fourth or one-third of a grain daily for days in succession. Almost never will a stomatitis follow, and no gastric or intestinal irritation, provided the dilution be in the proportion of at least 1:8,000. An occasional slight diarrhœa may require the addition of a few drops of camphorated tincture of opium. I can repeat a former statement, that never before the antitoxin period (see below) have I seen cases of croup getting well in such numbers, either without or with tracheotomy or intubation, as when under mercurial treatment. I would not be understood, however, to limit the use of mercury to laryngeal diphtheria; it has equal effects in that of the pharynx, and mostly in the streptococcic and in the mixed forms of diphtheria. In connection with this statement I wish to emphasize again the necessity of not relying on a single method of treatment in a disease so dangerous and whimsical as diphtheria. The self-complacent nihilism which relies exclusively on pathological research and laboratory methods has more than once impeded the medical and social and humanitarian position of clinical medicine. It is a pleasure, therefore, to quote an author who has won laurels in bacteriology: "The giving internally of the tincture of the chloride of iron or of the bichloride of mercury in small frequent doses has considerable local effect upon the mucous membranes of the throat and pharynx" (W. H. Park).

When, in laryngeal diphtheria, internal treatment proves unsuccessful, intubation or tracheotomy should be resorted to. A small, frequent, and intermittent pulse, aphonia, cyanosis, and marked retraction, with every inspiration, of the supraclavicular fossæ and the epigastrium, are most urgent indications for the operative procedure. They should not be allowed to last. I shall not here be tempted to defend the two operations; I shall not even be tempted to discuss the criminality of allowing a child to suffocate without resorting to mechanical relief, or to compare the two operations with each other. I can only say that for years I have not seen a case in which intubation would not take the place of tracheotomy, and have therefore not performed the latter. Intubation takes the place of tracheotomy in most cases; in none does it make it impossible when required in the opinion of the operator. The latter operation may be preferred or become necessary for the purpose of getting at the trachea and bronchi for the mechanical removal of membrane and other local treatment, rare though the cases be in which such procedures are attended with success. It is probable that the many secondary tracheotomies which are still performed in Europe when intubation is alleged to be insufficient will not be considered requisite in the future. Nor is it probable that Bokai's method of using intubation as an adjuvant to tracheotomy will be followed long even by that distinguished clinician himself. Since 1891 his practice has been first to perform intubation and then tracheotomy, removing the tube just before he makes his incision into the trachea.

In the vast majority of cases of pseudomembranous laryngitis the Klebs-Löffler bacillus is found; and all of them are, therefore, fit subjects for the use of the diphtheria antitoxin. Since its introduction both general and local (laryngeal) diphtheria have been greatly benefited. At its Washington meeting in May, 1897, the American Pediatric Society received the "Report of its committee on the collective investigation of the antitoxin treatment of laryngeal diphtheria in private practice." Its salient points are as follows: The number of cases reported during the eleven months ending April 1st, 1897, was 1,704—mortality, 21.12 per cent. The cases occurred in the practice of 422 physicians in the United States and Canada. Operations employed: Intubation in 637 cases, mortality 26 per cent.; tracheotomy in 20 cases, mortality 45 per cent.; intubation and tracheotomy in 11 cases, mortality 63.63 per cent. Number of States represented, 22, besides the District of Columbia and Canada. Non-operative cases, 1,036, mortality 17.18 per cent.; operated cases, 668, mortality, 27.24 per cent.

Two facts may be recalled in connection with these statements:

First, that before the use of antitoxin 90 per cent. of cases of laryngeal diphtheria required operation; under the antitoxin, however, 39.21 per cent. Second, that the percentage figures have been reversed: formerly 27 per cent. represented the recoveries; now, under antitoxin, this figure represents the mortality. The committee expects still better results when antitoxin will be administered earlier and in larger doses, and recommends that all patients with laryngeal diphtheria, being two years or over, should receive as follows: Two thousand units at the earliest possible moment, two thousand units after twelve or eighteen hours, unless there be an improvement, and the same dose twenty-four hours after the second dose, if there be still no improvement. Patients under two years should receive one thousand or fifteen hundred units.

Dr. Dillon Brown's personal experience being unusually large and carefully recorded, I add without comment the following figures reported by him. He divided his intubation cases into three classes: Previous to November, 1890; from November, 1890, to September, 1894 (calomel sublimation period); from September, 1894, to April 1st, 1897 (antitoxin period). Of 442 cases of intubation without calomel sublimations and without antitoxin, 27.3 per cent. recovered. Of 295 cases of intubation with calomel sublimations, 41.6 per cent.; of 69 cases of intubation with antitoxin, 67.8 per cent. recovered. Without sublimations, 10.1 per cent.; with sublimations, 13.2 per cent.; with antitoxin, 23.3 per cent. recovered. During the first year with antitoxin, there were recoveries after operation in 38.4.; during the second year in 62.9; during the third in 94.7 per cent. The apparently bad results during the first year were probably due to two causes: inferior antitoxic serums and insufficient doses.

Caillé sums up his personal experience as follows: "Tracheotomy and intubation cases, before antitoxin, 280 cases, 30 per cent. recoveries; 17 intubation cases, with antitoxin, 3 deaths. Over one-half of all laryngeal cases treated with antitoxin recovered without operation. In every case of acute progressive stenosis 1,500 to 2,000 units of diphtheria antitoxin should be administered at once, and the dose may be repeated in twelve to twenty-four hours, and so on until relief is manifest."

In Baginsky's hospital service there were 1,258 cases of diphtheria in the years 1890–94; 418 tracheotomies and 135 intubations were performed, with a total mortality in these 553 operations of 62 per cent. In the 418 tracheotomies the mortality was 64.4 per cent.; among these were 77 which were performed after intubation; these 77 had a mortality of 69 per cent.; 58 intubations without secondary tracheotomy had a mortality of 41.8 per cent. This condition of things changed with the inauguration of antitoxin treatment. No case of laryngeal stenosis developed in those in whom the remedy was injected before the larynx became affected. Thus it was that in 525 cases there were but 53 tracheotomies and 54 intubations, the former with 34 deaths, the latter with 2. It became necessary to perform tracheotomy after a previous intubation in 12 cases, of which 9 ended in death. The speedier disintegration of the membranes and the almost general discontinuance of their growth after the injection of antitoxin are the reasons why Baginsky has since preferred intubation to tracheotomy.

At that early time in which his results were published, Heubner performed 33 operations in 181 cases—viz., 23 tracheotomies with 52 per cent., 10 intubations with 80 per cent. recoveries—a remarkable improvement over the figures of the ante-antitoxin period.

At the International Congress of Moscow Monti made the statement that in his service cases of laryngeal stenosis were apt to get well under the sole influence of antitoxin, that an operation was resorted to only when that treatment proved unsuccessful (after some days), and even then was likely to be successful. Without antitoxin, in former times, his intubations would yield a mortality of from 25 to 40 per cent., now while antitoxin was employed, 12 per cent. Only in the "mixed" infections the mortality rose to 33 per cent.

It is useless to quote any more experiences in regard to the efficacy of antitoxin in diphtheritic stenosis of the larynx. In many cases it renders operations unnecessary; in those operated upon the prognosis is improved. Still many die; of those following "mixed" infections very many die. If there be those who shoulder the responsibility of relying on a sole remedy, which frequently heals and frequently fails, to the exclusion of every other helpful medication or contrivance, they are as short-sighted as those who still refuse altogether to acknowledge the great efficacy of antitoxin in diphtheria. The fanaticism of the one should not be permitted to justify that of the other. The satisfaction at having a powerful remedy like antitoxin should not engender the nihilism which begins after the subcutaneous injection of serum. This cannot be said too often, particularly in reference to "mixed" infections. It is only the bacillus part of the malady which can be counteracted by antitoxin. The mixed infections at least, with their virulence and danger, should not be left to die without medication beyond injection and "expectant" neglect.

Heart failure is usually developed gradually. It is foreshadowed by an increasing frequency and weakness of both heart beats and pulse, by an occasional intermission, by unequal frequency of the beats in a given period (say of ten seconds), or by the equalization of the interval between systole and diastole, and diastole and systole. This latter condition, which is normal in the embryo and fœtus, is always an ominous symptom; so is the too close proximity of the second sound (so as to become almost inaudible) to the first.

Heart failure is due, besides the influences common to every disease and every fever, to tissue changes in the myocardium, in its nerves, in the endocardium, and to the gradual formation of blood clots. These changes may be due to the malnutrition of the tissues resulting from every septic condition of the blood, or to specific alterations due to the diphtheritic process. Failure may come on after having given warning, or it may be on us without any. Thus, every case of diphtheria ought to make us anxious and afraid. Indeed, there is no safety and no positively favorable prognosis until the patient is quite recovered, and even advanced beyond the period in which paralysis may develop.

Whatever enfeebles must be avoided; absolute rest must be enjoined. The patients must be in bed, without excitement of any kind; they must take their medicines—which ought to be as palatable as possible—and their liquid food, and evacuate their bowels in a recumbent or semirecumbent position; crying and worrying must be prevented; the room must be kept airy and rather dark, so as to encourage sleep if the patients be restless; and restless they are, unless they be under the influence of sepsis, and thereby subject to fatal drowsiness and sopor. In no disease, except perhaps in pneumonia, have I seen more fatal results from exertion on the part of the sick, or from anything more fatiguing than a sudden change of posture. Unless absolute rest be enforced, neither physicians nor nurses have done their duty. The latter must avoid all the dangers attending the administration of medicines, injections, sprays, and washes. Preparations for the same must be made out of sight, every application should be made quickly and gently. On no account must a patient be taken out of bed for any of these purposes. I know of children dying between the knees of nurses who called themselves trained and had a diploma.

The use of pharmaceutical preparations, such as digitalis, strophanthus, sparteine, caffeine, besides camphor, alcohol, and musk, should not be postponed until feebleness and collapse have set in. These are at least possible, even probable, and it is certain that a cardiac stimulant will do no harm. It is advisable to use it at an early date, particularly in those cases in which perhaps antipyrin or antifebrin (the indications for which are certainly rare, as excessive temperatures are very exceptional) is given. Besides, it is not enough that the patients should merely escape death; they ought to get up, *cito, tuto, et jucunde*, with little loss and speedy recuperation; a few grains of digitalis or their equivalent—preferably a good fluid extract—may or should be given, in a pleasant and digestible form, daily. When a speedy effect is required, one or two doses of two to four minims each are not too large, and must be followed up by smaller ones. When it is justly feared lest the effect of digitalis be too slow, I give, with or without it, strophanthus, in doses of from one to six drops of the tincture, or sulphate of sparteine. Of the latter an infant a year old should take gr. $\frac{1}{10}$ or $\frac{1}{4}$ (6–15 mgm.) four times a day as a matter of precaution, and every hour or two hours in an emergency.

Of the same importance are alcoholic stimulants. The advice to wait for positive symptoms of heart failure and collapse before employing the life-saving apparatus is bad. There are cases which get well without treatment, but we do not know beforehand which they will be. No alleged mild case is safe until recovery has taken place. When heart failure has once set in—and it frequently occurs in apparently mild cases—our efforts are too often in vain. Thus alcoholic stimulants ought to be given early and often, and in large quantities, thoroughly diluted. There is no such thing as danger from them or intoxication in septic diseases—100 c.c. (℥ iii.) daily may suffice, but I have often seen 300 c.c. (℥ ix.) or more daily of brandy or whiskey save children who had been doing badly with 100 c.c. (℥ iii.).

Caffeine, or, in its stead, coffee, is an excellent cardiac tonic, except in those cases in which the brain is suffering from active congestion. For subcutaneous injections the salicylate (or benzoate) of caffeine and sodium, which readily dissolves in two parts of water, is invaluable for emergencies, in occasional doses of from gr. i.–v. (6 to 30 cgm.) in from ♏ ij.–x. of water. From gr. v.–xx. (0.3–1.25) of camphor may be given daily, as camphor water, or in a mucilaginous emulsion, which is easily taken. It does not so disturb the stomach as carbonate of ammonium is apt to do. For rapid effect it may be administered hypodermically, in four to five parts of sweet almond oil, which is milder and more convenient than ether. Strychnine may be added regularly from the beginning of danger, and mainly in cases with little increase of temperature. Its effect is more than momentarily stimulating. A child of three years will take gr. $\frac{1}{100}$ (0.5 mgm.) three times a day, and much more in an urgent case, and then subcutaneously. But the very best internal stimulant in urgent cases is Siberian musk. I prefer to give it from a bottle, in which it is simply shaken up with a thin mucilage. In urgent cases it ought to be administered in sufficient doses and at short intervals. When ten or fifteen grains given to a child one or two years old within three or four hours will not restore the heart's action to a more satisfactory standard, the prognosis is very bad.

Nephritis, parenchymatous, interstitial, and glomerular, and the varieties of *pneumonia* are frequent complications or consequences of diphtheria. The treatment of either of them requires no particular discussion in this place. Nor does *œdema of the glottis* yield indications differing from those of the same affection occurring from other causes.

Diphtheria of the *skin* and of the *sexual organs* requires disinfectant ointments. I have mostly relied on iodoform one part, in from eight to twelve parts of fat.

Diphtheritic *paralysis*, though of manifold anatomical and histological origin, yields in all cases a certain number of identical therapeutical indications. These are the sustaining of the strength of the heart by digitalis and other cardiac tonics. This is an indication on which I cannot dwell too much. Many of the acute, and most of the chronic, diseases of all ages do very much better by adding to other medications a regular dose of a cardiac tonic. While it is a good practice to follow the golden rule to prescribe simply, and if possible a single remedy only, it is a better one to prescribe efficiently.

Besides, there are some more indications: mild preparations of iron, provided the digestive organs are not interfered with; strychnine, or other preparations of nux vomica, at all events; in ordinary cases a child of three years will take gr. $\frac{1}{80}$ three or four times a day (together 0.002 gm.). Local friction, massage of the throat, of the extremities, and trunk, dry or with hot water, or oil, or water and alcohol; and the use of both the interrupted and continuous currents, according to the known rules and the locality of the suffering parts, find their ready indications. The paralysis of the respiratory muscles is quite dangerous; the apnœa resulting from it may prove fatal in a short time. In such cases the electric current used for short periods, but very frequently, and hypodermic injections of sulphate of strychnine in more than text-book doses, and frequently repeated, will render good service. I remember a case in which these, with the occasional use of an interrupted current, and occasional artificial respiration by Sylvester's method, persevered in for the better part of three days, proved effective. In a few cases of diphtheritic paralysis the use of antitoxin appeared to score a success. Other forms of paralysis (hemiplegia, ataxia) demand a treatment like the above, modified by their peculiar circumstances or symptoms.

Orrhotherapy.—The use of diphtheria antitoxin has been discussed several times on previous pages, mainly as regards its effect as an immunizing agent and its action in laryngeal diphtheria. It has passed its experimental stage as safely as if it had been employed these fifty years, and has created a literature of its own on which bacteriologists, chemists, medical and surgical clinicians, practical men and theorists, friends and enemies have been at work. No matter what the nature of its action may be, whether when injected under the skin of a diphtheria patient it supplements the antidote created by the toxin of diphtheria in the blood or the cells of the patient, or whether it aids the antitoxin into which the toxin is believed by some to be changed (Bucher, Smirnow, Metchnikoff) or which is the product of reaction (Behring, Ehrlich *), this action can no longer be doubted. Discussions on that point are fruitless. When the injection is to be made, the syringe should be sterilized each time, for no piston is entirely safe. A carbolic-acid solution of five per cent., and absolute alcohol will suffice for that purpose. The injection should be made into a loose and copious subcutaneous tissue, not into the skin, and not into muscles. The abdomen is more sensitive than the lumbar region and the thigh, and the subscapular or intrascapular region. The latter should not be selected unless the subcutaneous tissue is quite abundant. According to the severity of the case six hundred, one thousand, fifteen hundred, or two thousand "units" should be injected. The dose should be repeated unless the symptoms—both constitutional and local—be improved within twelve or twenty-four hours. Sixty-five hundred units were successfully used in a bad case of noma of the vulva, in which diphtheria and putrefactive bacteria were found by Petrushky (*Deutsche medicinische Wochenschrift*, 1898). The puncture should be covered with an antiseptic gauze, or with iodoform collodion.

A "unit" is equivalent to 1 c.c. of what is called "normal serum." Normal serum is the blood serum of an immunized animal which was made so efficacious that 0.1 c.c. antagonizes ten times the minimum of diphtheria poison fatal to a guinea-pig weighing 300 gm. (about 10 ounces).

The universal demand is for early injection. There is unanimity in the experience that the prognosis is impaired by procrastination. The latest report from Vienna is only a repetition of what has been known these four years. When antitoxin was injected on the first and second day, only 6.7 per cent. of all the cases died, on the third 19, on the fourth 23, on the fifth 31, on the sixth 33.3 per cent.

This fact has become so fixed in the minds of many practitioners who believe themselves responsible for the welfare of their patients, that in doubtful cases in which the diagnosis of "diphtheria" or "pseudodiphtheria" has not been made on account of time, and in view of the innocuousness of antitoxin when injected unnecessarily, and believing that whatever discomforts there may arise after the injection do not compare with the danger of the disease when not combated in time, they "inject the antitoxin and settle the question of diagnosis afterwards" (Charles G. Jennings in *Medical Age*, February 25th, 1898). In general that practice is to be recommended in bad cases and bad seasons, for the bacteriological diagnosis can be completed before another injection is required, if at all.

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* Erhrlich thinks the antitoxin is the result of functional overexertion of the cell protoplasm which has been irritated by the circulating toxin, and compares this process with the hypertrophy of overexerted organs.

All forms of diphtheria are liable to be benefited by antitoxin, from the simplest to the septic, from the uncomplicated to the mixed, the latter less than the former. It is this mixed form in which I look upon the neglect of other treatment, both local and general, as simply criminal. The statistics both of hospitals and of private practice have grown immensely, and are daily growing; they are the staple article of our journal literature. I would therefore refer the reader to what I quoted in my "Therapeutics of Infancy and Childhood," and will conclude with a few of those data which are quite recent.

Of the report of the diphtheria committee of the Clinical Society of London *The Lancet* (June 4th, 1898) publishes what follows:

"For the purpose of the inquiry 832 reports of cases were collected, but upon examination 199 of them had to be rejected, either because the committee were not satisfied as to the evidence of diphtheria or because the amount of antitoxin administered was not stated in normal units, leaving 633 available for further analysis. Of the cases which presented symptoms more or less severe of laryngeal affection nearly one-half escaped the operation of tracheotomy, a very much larger proportion than is usually the case in laryngeal diphtheria treated in other ways. The tracheotomies performed may be divided into two groups: (*a*) Tracheotomy within twenty-four hours of the first injection, and (*b*) tracheotomy at a later period. Only 2 out of the 75 belong to group (*b*). The committee drew especial attention to these facts, and also to the results of the operation of tracheotomy, in which the mortality amounted to 36 per cent., as opposed to 71.6 per cent. in the control series compiled from the records of the general hospitals before the introduction of antitoxin. The mortality fell as age increased, but it was in the first five years of life that the lessened mortality in the antitoxin series was most marked. It was to the lesser frequency with which membrane extended to the larynx and trachea in cases treated by antitoxin and to the effect of the antitoxin on them when membrane was present that the lessened mortality in the antitoxin series was mainly due. The total mortality in the 633 cases amounted to 124, or 19.5 per cent., as opposed to 29.6 per cent. in the non-antitoxin control series. Not only was the mortality in the antitoxin series much less than in the other, but the duration of life in the fatal cases was longer, a fact which has considerable bearing on the frequency with which paralytic symptoms occurred. The closest investigation failed to discover any connection between the occurrence of paralysis and the amount of antitoxin injected, nor did the period of the disease at which it was first used appear to exert any influence on the occurrence of paralytic symptoms. Some form or other of rash followed the injection of antitoxin serum in very nearly a third of the cases. The rashes could be divided into two main types: those which were of an erythematous and those of an urticarial character; the former largely predominated. In no instance did the presence of a rash appear to have any bearing on the ultimate result of the case. Joint pains which were not met with in the non-antitoxin series and were apparently due to the antitoxic serum were observed in a small number of cases. The percentage of deaths with suppression of urine was found to be practically the same in the antitoxin and the non-antitoxin series. The general result of the inquiry showed that in the cases treated with antitoxin not only was the mortality notably lessened, but the duration of life in fatal cases was also prolonged. The injection of antitoxin may produce rashes, joint pains, and fever; with these exceptions no prejudicial action has been observed in the series of cases investigated to follow even in cases in which a very large amount of antitoxin serum has been used."

According to Buchwald (*Münchner medicinische Wochenschrift*, 1898, No. 14) of 563 patients treated without antitoxin, 57.72 per cent. died; of 311 treated with it, 28.93 per cent. died. Tracheotomies were required in 57 per cent. in the ante-serum period, in 30.86 per cent. during the serum time. Albuminuria was observed in 36.65 per cent. of all the injected cases, paralysis in 93 cases, exanthems in 74, pain in joints, without swelling however, in 2, otorrhœa in 10, bronchopneumonia in 36 cases. Most of the latter were fatal. Besides antitoxin, good nutrition, stimulants, and irrigation of the nose and mouth were employed.

Axel Johannessen communicated to the Moscow Congress a report covering 1,131 cases of diphtheria observed during 1890 by 71 Norway physicians. Those cases were treated with antitoxin; there were 73 deaths (6.5 per cent.); this percentage is reducible to 5.3 per cent. by deducting the cases that came under treatment while moribund. From 1867 to 1893, before the antitoxin period, the mortality was 23.5 per cent.

Escherich had in Prague a mortality of 9 per cent., compared with 36 per cent. of former times.

John E. Walsh (*New York Medical Journal*, June 18th, 1898) publishes the following figures. In 1895–96 there were treated in the District of Columbia—

Cases with antitoxin, ...174; died, 23 = 13.2 per cent.
Cases without antitoxin, 152; " 53 = 34.9 "

In 1896–97 there were

Cases with antitoxin, ...285; died, 21 = 7.3 per cent.
Cases without antitoxin, 335; " 89 = 26.6 "

Of the 285 antitoxin cases there were 238 below twelve years, with a mortality of 8.9 per cent.; of the 335 non-antitoxin cases there were 256 below twelve years, with a mortality of 33 per cent. Of 86 over twelve years treated with antitoxin none died; of 113 of the same age treated without antitoxin, 8 died. In the last seven months preceding the publication 422 cases were treated: 211 with antitoxin and a mortality of 8, or 3.8 per cent.; 190 without antitoxin and a mortality of 65, or 34.2 per cent., as in the pre-antitoxin period. The treatment employed in 21 cases was unknown to the writer.

Among the very latest statistics are those of Krönlein (Zürich), who reported to the Twenty-seventh Congress of German Surgeons (April, 1898) on 1,773 cases of diphtheria observed in the clinical hospitals of the university during the years 1881–97. A recapitulation of the results is presented in the following table:

	PRE-ANTITOXIN PERIOD.			ANTITOXIN PERIOD.
	"Old croup room." 1881–1889.	New diphtheria house. 1889–1894.	Total. 1881–1894.	New diphtheria house. 1894–1897.
Total	485	851	1,336	437
Deaths	230	304	534	55
Mortality	47.4%	35.7%	39.9%	12.5%
Operations	354	308	662	17
Deaths	211	227	438	36
Mortality	59.6%	73.7%	66.1%	35.6%
Cases not operated	131	543	674	336
Deaths	19	77	96	19
Mortality	14.5%	14.1%	14.2%	5.6%

In all the 437 cases in the antitoxin period the Klebs-Löffler bacillus was demonstrated. Krönlein's statistics prove the following facts: While the morbidity of the whole district (city and country) remained unaltered in the antitoxin period, the mortality decreased considerably—mainly in the surgical clinic, in operated (tracheotomy or intubation) or non-operated cases, and principally in the first years of life. While previous to the institution of antitoxin treatment one-half of all the cases had to be operated upon, this percentage has fallen to 23.1 per cent. since that time.

After the injection of antitoxin improvement set in speedily; the temperature diminished; the deposits on, and the membranes in, the throat and air passages soon loosened, and the diphtheritic secretion of the nose became speedily less; the lymphadenitis of the neck diminished; the diphtheria process did not descend into the air passages; mild laryngostenosis did not increase; there was no diphtheric infection of the tracheotomy wound, which was observed in one-third of all the cases of former times; and the tube could be removed as early as the third, fourth, or fifth day after tracheotomy.

During the same period albuminuria was observed in 36.6 per cent. of all cases of diphtheria, pronounced nephritis in 4.6 per cent., and postdiphtheritic paralysis in 12.5 per cent. Exanthems of the most various forms, with mild general symptoms only, were met with in 8 per cent.; they were attributed to the serum. None was found after small injections made for the purpose of immunizing healthy persons.

To gainsay, with such statistics at hand, the superiority of antitoxin to any other single remedy known to us for diphtheria is a foolhardy undertaking. But there are some drawbacks met in its employment which are acknowledged by all, and exaggerated by some. I refer to disagreeable symptoms with which the administration of antitoxin is charged, and which are said to take place in the blood, on the skin, in the joints, in the respiratory, circulatory, urinary, digestive, and nervous systems. Even sudden death has been claimed as one of the results of antitoxin injections.

Dr. James Ewing studied the effects of antitoxin on the number and nature of *leucocytes* (*New York Medical Journal*, August 17th, 1895). While leucocytosis begins a few hours after the invasion of diphtheria, and increases mainly as regards myelocytes (uninuclear and neutrophilic granules which are never found in the lymph nodes) up to the climax of the disease, and steadily declines during convalescence—remaining high only in most of the bad and fatal cases—antitoxin causes, according to Ewing, a reduction of the number of leucocytes within thirty minutes after the injection. This reduction affects mainly the uninuclear leucocytes, while the proportion of well-stained multinuclear cells is increased. In favorable cases the leucocytosis never again reaches its original height after the injection; in severe and very bad cases it is followed in a few hours by more leucocytosis and fever. In very bad cases the immediate result may be either rapid increase or decrease of leucocytes, and death. The multinuclear leucocytes found in the blood in favorable cases after treatment with antitoxin show an increased affinity for gentian violet. This change may be observed within twelve hours after the injection, and its non-occurrence is a very unfavorable prognostic sign.

John S. Billings, Jr., found after the employment of antitoxin some little diminution in the number of blood cells. In six cases so treated he met with a steady rise, and the decrease of hæmoglobin was less marked than in cases of uninfluenced diphtheria.

Urticaria, sometimes with increased temperature, pure or complicated with *erythema* (simple, or multiform, or exudative with or without extravasation) is observed at different times, very soon or a few days after the injection round the puncture, or after one or more weeks in different parts of the body. Now and then the efflorescence requires some predisposition, for it has been noticed in one child of a family while the rest remained free. Horse serum containing no antitoxin is known to have caused the same eruption; this effect appears to be more marked in the serum of one horse than in that of another. It is similar to what has been observed after transfusion of the blood of heterogeneous animals. The small amount of carbolic acid contained in the antitoxin should not be held responsible for the eruption; nor can the local irritation be charged with causing eruptions which take a week or weeks to develop. Altogether this urticaria behaves like the vasomotor or neuropathic cutaneous irritations observed in predisposed persons after the use of oysters, crabs, or strawberries.

Herpes (nasal, labial, aural) has been noticed in a few instances, notably by Baginsky, and by Mya, who observed at the same time a "critical" fall of the temperature of the body.

Other forms of eruptions, macular, papular, and erythematous, also petechiæ with or without larger extravasations, have been recorded. Desquamation is observed in proportion to the degree of dermatitis. Some observers speak of many cases, others of few, others (Rumpf) never saw any eruption.

W. T. Coues reports fifty cases of antitoxin injections for the purpose of immunization. A child of five years received five hundred units, a baby of one day fifty, those under six months three hundred, under a year four hundred. The older children were not affected in the least; the infants were restless and cried long after the injection. The temperature of three infants reached 101° F. five hours after the injection; the next morning it was normal. On the morning following the injections the younger children had slight coughs, which passed away in two or three days. Urticaria occurred in 14 cases out of the 50 injected; a punctated erythema in 2; in 1 there were soreness and pain in the right knee-joint, which passed off in two days (Boston *Medical and Surgical Journal*, July 14th, 1898).

Abscesses, occasionally with lymphangitis, have been observed by Monti, Variot, and others. When they occurred, fault was found with the serum which was not considered germ-free, or with the skin which was charged with not having been aseptic, or with the undue thickness of the needle and subsequent infection of the wound, or with the perforation of too many layers of tissue down into the muscles, or with the condition of the syringe, which it is difficult, no matter whether the piston is leather or asbestos, to render absolutely safe. In a few instances symptoms were observed which were attributed to the entrance of air into a small vein.

Arthropathies were noticed with or without exanthems. Swelling and pain of a knee or an ankle-joint were noticed a few times, together with urticaria in the second week after an injection. These lasted a day or a week or more. They are not frequent, for there are observers who have never seen them in any of a large number of cases. It should not be forgotten that they are symptoms which occasionally occur in diphtheria not treated with antitoxin.

Lymph bodies now and then swell after an antitoxin injection, but only in connection with an eruption or an arthropathy.

Antitoxin has been charged with causing *pneumonia*. The latter is so frequent a complication of diphtheria in all its stages that the attempt to substantiate the charge seems hazardous. If antitoxin affects the mucous membranes favorably it is not likely to produce bronchitis or pneumonia. Possibly Lennox Browne feared this alleged effect when he considered the use of antitoxin contraindicated during the existence of a bronchopneumonia.

It has also been accused of developing a latent *tuberculosis* into one of more rapid progress. That is barely possible inasmuch as every fever, for instance after vaccination, is held to have a similar effect. But it is very much more probable that the invasion of the Klebs-Löffler bacilli and of the streptococci of the diphtheritic attack, according to previous statements referring to their complications with tubercle bacilli, leads to the outbreak.

A secondary *fever*, lasting a day or longer, has been observed after ten or fourteen days; it often coincides with an eruption of urticaria, and seems to be a legitimate symptom of the latter. In most cases, however, another etiology is more probable. It is more often connected with the diphtheria than with the antitoxin treatment. In many cases there may be a new invasion, mostly of cocci; there may be an abscess, a rhinitis, a tuberculosis. With an abscess, or still more commonly with rhinitis, lymph bodies will swell and the temperature will rise.

After an injection of antitoxin *vomiting* and *diarrhœa* have been noticed and have been explained as the result of intoxication with a fibrin ferment. On the other hand, Baginsky is positive that he has seen those symptoms less often after antitoxin than in cases of diphtheria not so treated. It appears not improbable that the blind confidence in antitoxin has something to do with an occasional case of gastrointestinal irritation. For with some every other treatment is neglected, while antitoxin is being administered, and it is quite possible that abundant membranes not removed by irrigation, while being rapidly loosened and thrown off, are swallowed.

Albuminuria and *nephritis* are not at all met with after the injection of antitoxin by some observers (Riether in none of 1,450 cases); frequently by others (Soltmann in 72 per cent.). They occur within a week. Sörensen reports no albuminuria when he operated with Danish serum, but many cases after the use of French serum. That experience would go to show that either the normal horse serums were different, or that the preparation of the antitoxin was not identical. The small amount of phenol contained in it should not be accused, for it is too minute even to be discovered in the urine. What should not be overlooked is the fact that both albuminuria and nephritis are common occurrences, beginning in the very first week of a diphtheria, sometimes within a few days, before antitoxin is administered or has had time to take effect. Among 181 cases of Heubner's of those injected on the first day of the disease five-sixths remained free; on the second, two-thirds; on the third, one-half; on the fourth, one-third. In 525 cases of Baginsky's treated with antitoxin there was albuminuria in 40.95 per cent., clinical nephritis in 12.57 per cent., and post-mortem nephritis in 15.80 per cent. However, among 933 treated without antitoxin there was albuminuria in 42 per cent., clinical nephritis in 25.78 per cent., and post-mortem nephritis in 16.31 per cent.—rather a favorable showing for antitoxin. In Strassburg (Sieger, in Virchow's *Archiv*, 1897) renal affections were frequent after the injection of antitoxin; but though some of them lasted weeks or months, they were benign and without morphological elements in the urine.

In some cases albuminuria will change, either totally or partially, into albumosuria, under what appears to be bacterial or antitoxin influence.

The existence of the after-effects is not denied by any of the most enthusiastic admirers of antitoxin, but it is claimed by all that no serious or lasting bad results follow, and that if every life threatened by diphtheria were known to be protected by the alleged untoward or uncomfortable effects of the remedy, we should willingly submit to them in every case. The balance of what we know of antitoxin is thus far favorable, and this addition to our therapeutical powers will forever be remembered as creditable to Emil Behring. The lack of recognition which was some time ago withheld from him by many was, most unfortunately, his own fault. The morbid vanity and some personal motives displayed in almost every one of his writings tallied so badly with the tendencies and the spirit of a scientific benefactor as to render suspicious both his veracity and his motives.* Still, the grateful medical profession and the public will not forget his work. That his preoccupation and his limited horizon should dwarf his judgment is a matter of regret. It is a pity he is not a clinician, but only a scientific famulus. If he were a clinician he would not have been tempted into asserting that organotherapy has accomplished nothing, that cellular pathology has proved sterile, that remedies combat main symptoms only, that medicine has had hitherto therapeutical principles only but no therapeutical experimentation, and that his experimental therapeutics is in conscious opposition to medication (German Congress for Internal Medicine, June, 1897).

Behring himself explains the occurrence of undesirable effects of his serum only by the accidental and indifferent albuminoids and salts contained in the serum. They are according to him greatly reduced by increasing concentration, even to the dry state which he succeeded in obtaining. In the concentration the antitoxin is "absolutely uninjurious, without poisonous effects in man or animal, healthy or sick." According to H. C. Ernst, J. N. Cooledge, and H. A. Cooke (*Journal of the Boston Society of Medical Science*, May, 1898), the antitoxic property of antidiphtheritic serum can be removed from one part of the serum and added to another by a method of fractional freezing, the bottom layers showing greater strength. By this method serum of high potency, more or less permanent, can be obtained.

Like Behring, Henry W. Berg (*Medical Record*, June 18, 1898) attributes undesirable effects, eruptions following the administration of antitoxin, to some original adulteration. "It is probable, almost certain, that many of the eruptions are due to a toxalbumin contained in the serum of the horse which should be strained through a fine Chamberland filter. Neither the pure serum of the horse nor the diphtheria antitoxin loses any of its power by filtration."

The adversaries of antitoxin have tried to make it responsible for diphtheritic *paralysis*, without any reason. It is true that there are many cases of paralysis occurring in children previously treated with antitoxin, but it has always appeared to me that the number was swelled by some of those who would have succumbed without antitoxin long before the period of paralysis was due. Apparently mild cases of diphtheria are followed by paralysis; it is certainly true that many a case is changed into a mild one by antitoxin. It is after all better to have a paralytic child with the great probability of a final recovery than a corpse without even a chance of paralysis. Moreover, I cannot imagine a more difficult task than to calculate statistics on totally absent bases. The average number of paralyses varies according to the cases, the severity of the epidemics, and probably to the treatment also. And finally, large numbers of cases, like those of Baginsky, appear to prove the contrary of what has been alleged. Among 993 patients before serum therapy was introduced there were 68 cases of paralysis, or 6.8 per cent.; among 525 in the antitoxin period there were 27, or 5.14 per cent. Schmidt Rimpler feels certain that his patients with accommodation paralysis recovered more speedily under the use of antitoxin than without it.

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* This was written in the first edition of my "Therapeutics of Infancy and Childhood" some years ago. Those who thought I was too severe in criticising the motives of the man have since learned that he has obtained in this country, where no physician deigns or would dare to descend into the arena of bargaining and shopkeeping, a patent right on his wares, which I am credibly informed secured him more than a million marks in a single year in his country.

Sudden deaths have occurred after the injection of antitoxin, the doses being in some instances quite small. The case of the Langerhans child in Berlin, who died after having received an injection of antitoxin, is not explained in spite or because of loud vituperations and vilifications. Most reporters of cases have been satisfied with admitting they know of no explanation. Belin publishes one of the latest cases, and admits that death cannot positively be attributed to the influence of the serum. Nifong (*Medical Review*, May 7th, 1898) gave a boy of fifteen years, of slight build and with feeble circulation, fifteen hundred units. After ten minutes there were pallor, numbness of the extremities, cyanosis, swelling of the face, and vomiting. Death occurred in thirty-five minutes. Two girls received the same dose of the same serum obtained from the city chemist of St. Louis without a bad result.

Rauschenbusch observed on his four-year-old daughter, who had taken three times the dose while sick with diphtheria two years previously, pruritus, urticaria, vomiting, sopor, and heart failure after two hundred units injected for the purpose of immunization. It does not appear that a connection between heart failure and sudden death on the one hand and antitoxin on the other has been established in any case, and venturesome and generalizing speculations are not able to shed light on obscure subjects. At all events, a single finding, a suggestion, or a suspicion of vomiting and aspiration of a solid body into the air passages, or of the injection of air into a vein, or excitement and fright, or a lymphatic state, or a large thymus, if at all applicable to an individual case, does not permit of a universal interpretation.

After all, we can well agree with the conclusions of Dieudonné when he says that the treatment of diphtheria with serum is an essential advance in therapeutics, that its effect is more frequently favorable than that of former methods, and that accessory consequences do not outweigh the useful effects.

H. Biggs recapitulates many of his previous writings in a paper read before the Society of the Alumni of Bellevue Hospital, as follows: "Since the introduction of antitoxin treatment the mortality of diphtheria is reduced to one-half, its course is shorter and milder; an injection made within the first two days reduces the mortality to five per cent.; the earlier it is made the better the result. Small quantities of concentrated serum are tolerated by the very youngest babies. If antitoxin is not a specific it is certainly the best remedy in our possession against diphtheria. The genuine (that is, uncomplicated bacillary) cases are more amenable to its favorable influence than mixed infections. It has no secondary effects on heart, kidneys, or nerves. Heart failure and paralysis whenever observed are caused by diphtheria, not by antitoxin."

TETANUS.

BY

VICTOR BABES,

BUCHAREST.

TETANUS.

A DISEASE like tetanus with such mysterious and terrible symptoms and in which a fatal issue is so frequent, was of course observed in the earliest times, especially as the disease naturally occurred more frequently during the ancient wars than it does to-day in civilized countries.

History.

Hippocrates remarked that the disease was an extremely dangerous one, occurring in all climates, at all periods of life, at all times, during war or peace, but especially in war.

We also find the disease described by Galen, Celsius, and Aurelian. Aretæus mentions especially three forms: tetanus, opisthotonos, and emprosthotonos, of which the latter certainly does not belong to tetanus.

Maitre and Fragault especially mention the disease as occurring after operations, and we also find tetanus mentioned in the wars of the last century as a result of gun-shot wounds.

We find many cases of the disease described, especially as occurring among the aborigines in the tropics. But in regard to the knowledge of it and its diagnosis in times of peace, we observe much uncertainty even in this century. Even Romberg who recognized the nervous symptoms of tetanus as such, considered the tetanus symptoms as reflex convulsions, and often we find cerebrospinal meningitis, eclampsia, maxillary affections, and even abscesses confused with tetanus.

It was those of the Parisian school, Dupuytren, Fernel, Lange, Boyer, and Verneuil, and then the Germans Friedrich, Romberg, Rose, Louis Henner, and Billroth who recognized the nature and character of tetanus and interpreted the symptoms properly. Especially Verneuil long ago laid stress on the infectious character of the disease, and maintained that the poison was conveyed by horses, which in reality often suffer from tetanus.

Rose, whose description of the various forms of tetanus we shall follow quite closely, is entitled to great praise for his clear recognition of the nature of the disease; and the modern bacteriological researches which have revealed the true etiology of tetanus, have at the same time confirmed his clinical observations in great part.

According to the results of modern researches we may to-day regard tetanus as a disease which is due to a toxin produced by the tetanus bacillus, which excites a nervous irritation starting from the cerebral nervous system, particularly from the motor centres that have become hypersensitive. This induces a powerful tonic contraction of the muscles.

Etiology.

Tetanus is probably produced exclusively by the products of the tetanus bacillus. This bacillus is diffused widely over the world. Nicolaier first demonstrated that pieces of earth of the size of a pea, taken from a street in Göttingen, when subcutaneously introduced into the tail of a mouse produced tetanus after a few days, and that other mice could be infected later from the first mouse. Earth from the forest near Göttingen or from the clean yard of the Hygienic Institute did not produce tetanus.

Since that time these experiments have been repeated in most countries, and it has been proven that especially the earth in stables or streets, near polluted streams, or near the sea, produces tetanus, while this is not the case with earth near clean stables, in forests, or in gardens.

In Bucharest we have found earth containing the tetanus infection in the stable of our Veterinary School, in the streets, and on the banks of the Dimbovitza River, while earth from the barracks yard, from stables, from places where garbage or refuse was heaped, and from various gardens produced not tetanus, but sepsis.

It is advisable to make these experiments on guinea-pigs or on mice, because rabbits are less susceptible.

It is interesting to note that places in which the soil produces tetanus retain this characteristic for years. This probably explains the fact that the natives of certain tracts along the seashore or marshes, as in New Caledonia, in the Hebrides Islands, etc., for long periods of time, tipped their arrows with earth taken from certain regions, which produced violent tetanus.

I am convinced that the earth of old walls and the wood of old manure wagons rarely contain the tetanus infection, nor is horse manure always productive of the disease, but in two cases occurring in the human subject I found that inoculations with the fæces gave rise to tetanus.

It also has been shown by various investigators that not only may the dust of hay, of old houses, or cobwebs from stables produce tetanus, but healthy persons and animals may also carry tetanus bacilli in and on themselves. Thus Parietti and others have found them on old shoes, they have also been found in the dirt of finger-nails (Babes), in the discharges from healthy animals (Sanchez-Toledo), and rarely in those from human beings (personal observation). This is explained by the experiments of Sormani, who observed that tetanus bacilli may pass through the alimentary canal without being changed, as also by the fact that the intestines offer a favorable soil for an increase of the tetanus bacilli.

Numerous experiments show that there are stables where tetanus is produced very often and that even healthy animals are covered with the specific bacilli in such places. These fall off during the combing of the horses and may infect others. In these stables everything becomes infectious, the manure, the walls, the dust, the utensils, and even the clothing of the hostlers. In such a stable I have found the bacilli on the skin and in the manure of a horse which died from spontaneous tetanus, after another horse had succumbed shortly before to traumatic tetanus. This case and others in which the bacilli were found in the excrement of people who died from the disease prove that there are certain conditions under which the bacilli may grow exuberantly and acquire greater virulence, giving rise to local epidemics of tetanus; and this is especially liable to occur during war.

The propagation and increase of the tetanus germ are probably favored by various circumstances. In some cases the bacillus enters the earth from the animals suffering from the disease. But this way of infecting the soil is not the most important one.

Our experiments with buried decomposed bodies of animals and persons dead from tetanus showed in only one case out of six an increase of bacilli during decomposition. I also observed that when numerous bacilli were injected into dead animals hardly any were found after the animals had been buried two weeks. On the other hand, the tetanus germs in the earth are often increased in numbers by the presence of organic matter combined with a sufficient degree of heat.

We have no reason to assume that the ground will always become infected by cases of tetanus. The bacillus grows solely in diseased or decomposing organs, but not in the healthy body, and it proliferates only in circumscribed and restricted localities. On the other hand, tetanus spores remain virulent for years, and under favorable conditions may germinate rapidly outside of the body. I have found the spores remain very virulent, after being dried on threads or on wood, for two and one-half years without any special protection. It is also known that tetanus spores, after they have been brought into any locality, may remain virulent for years. This is especially shown by some epidemics which frequently recur in certain rooms and hospital wards.

The dust of such infected localities may contain the germ and may carry it through the air, not alone to the surface of the body and into wounds, but also into the air passages and the intestinal canal. But while the intact mucous membranes usually do not permit the entry of the tetanus bacilli, an inflamed or abnormal mucous membrane is less resistant, and we may in this way explain some cases of so-called idiopathic or rheumatic tetanus, as well as some cases occurring as complications or sequelæ of certain internal diseases.

During the discussion of the various forms of tetanus we shall have something more to say in regard to their origin.

BACTERIOLOGY.

The tetanus bacillus forms with others a group of moderate-sized rod bacilli which stain by Gram' s method. They are characterized by the presence of round terminal spores which are larger than the rods (drum-stick variety). With careful treatment it is found that in the cultures they form peculiar long pedicles with bell-shaped terminal branches. Upon these extremities are situated the spores.

The tetanus bacillus was first discovered and experimented upon by Nicolaier, later it was found by Rosenbach in human tetanus, but Kitasato was the first who succeeded in making pure cultures.

The bacillus appears as a slender mobile rod (especially on the heated object-glass), 0.3–0.5 μ in thickness and 2–4 μ in length. But we often find longer and thicker rods in the cultures. The spores are of various sizes, sometimes 0.8–2 μ in diameter, occasionally oval, but usually spherical in shape.

The bacillus stains with all basic aniline dyes, especially well by Gram's method, while the spores are also stained at first at the periphery; the fully developed spores may be stained by Ehrlich's method.

To isolate the bacillus from the wound Kitasato makes smear cultures from the pus on an agar plate, keeping it at a temperature of 37° C. for one or two days, raising the temperature to 80° for one hour, and then making anaerobic cultures from this material. By this process we sometimes succeed in separating the bacillus from the other bacteria which are contained in the same wound. I employ the following method: After preliminary culture under the surface of agar-agar the pus is heated to 80°, then again inoculated with the material under the surface of agar-agar and cultivated in a space devoid of air. If, at the end of three days and at the temperature of the body, fine rays or clouds have developed, extending laterally from the inoculation puncture, the test tube is heated somewhat, and the agar plug is poured into a sterilized dish. Agar-agar is then again inoculated with particles from the rays which ordinarily contain spores of the tetanus bacillus.

The bacillus grows slowly at the ordinary temperature of the room, more rapidly at the temperature of the body at which it forms spores after two days. In gelatin it forms golden-yellow points from which rays emanate. The medium is slowly liquefied in agar-agar, also in acid nutrient media it forms at the lower point of the puncture a whitish line, from which fine rays or clouds emanate. In bouillon it produces cloudiness. In milk it grows without affecting the fluid. In all cultures we observe a sharp, acrid odor, and some formation of gas.

The question whether the tetanus bacillus may grow under certain conditions aerobically is not yet fully settled; but it is asserted by some that cultures may be made to grow aerobically by repeated transplantations, with a loss, however, of their virulence as well as of their characteristic form; so that the question arises whether there are real tetanus bacilli in the aerobic cultures or whether we have to do with another variety cultivated at the same time. My own experiments seem to be more conclusive; I repeatedly made new cultures of the bacilli of the superficial layer, in which the microorganism grew gradually more superficially, but it never formed superficial cultures exposed to the air.

The virulence of the bacillus varies and is difficult to estimate, the more so because we have to take account of the action of the toxins in the production of tetanus. Older cultures with concentrated toxins will therefore often produce quicker and more virulent tetanus than recent cultures.

There are undoubtedly cultures which produce less poison in the same medium than others. Thus I have cultivated a bacillus from the pus of a horse which died from tetanus, which formed smaller and more oval spores and very virulent toxins, about ten times as virulent as those from a culture by Kitasato.

The bacilli gradually lose their virulence under certain conditions. Thus we get cultures at higher temperatures, with the addition of antiseptics (salts of iodine, carbolic acid, creosote), and especially under the influence of direct sunlight, which grow slowly and contain hardly any traces of toxins.

The toxin itself is also susceptible of modification. Thus it may be destroyed by carbolic acid, by a temperature of 55°-60° C., by long keeping, and especially by sunlight. If kept dry, it lasts longer.

We shall return later to a discussion of the toxins. The question whether the tetanus bacillus may produce toxins and cause tetanus alone, without any favoring circumstances, is not yet definitively decided. But it is certainly necessary to weaken the infected locality in order that the poisonous effect of the tetanus bacillus may become manifested.

Vaillard, Vincent, and Rouget have demonstrated that small quantities of tetanus spores, in which the toxin has been destroyed by heating, do not produce tetanus. But we see tetanus produced if we inject massive quantities, which also have a traumatic effect, or in other traumatic lesions, or after irritation by splinters of wood or lactic acid, or when other bacteria have prepared the soil, because the spores grow in the weakened tissue and form toxin.

I succeeded in producing characteristic tetanus in all the mammals experimented upon and in most birds with my very virulent bacillus, while formerly dogs and cats were considered not susceptible; but usually the results were not fatal in the latter. The course of tetanus is especially characteristic in pigeons; chickens show more resistance; I was also able to produce characteristic tetanus in the frog, if I kept it at a temperature of 30° C. The symptoms (which were here especially rigidity of the anterior and later also of the posterior extremities) began three to six days after the infection. The most susceptible animals are mice and guinea-pigs. In experimentally produced tetanus of mice, rats, and guinea-pigs we observe (after infection with culture in from one to three days, after injections of toxins sometimes within twenty-four hours) rigidity of the extremity nearest the seat of the injection, which gradually spreads to the other side and to the rest of the body, progressing from below upwards. The rigidity is increased by concussion or by irritation of the animal and is interrupted by clonic convulsions. In less susceptible animals and with smaller doses of toxin we observe tetanus of long duration, less pronounced, and often ending in recovery. Post mortem we find few changes; usually a little hemorrhage or induration at the point of inoculation, and it is difficult to find bacilli. We also find sometimes bacilli in the lymphatic glands of the neck. The blood, the urine, and the organs of the animals contain small quantities of tetanus toxins. Sometimes inoculation with the bowel contents produces tetanus.

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A singular property of the nervous system of mice which died from tetanus was observed by me, but I have not yet been able to explain it satisfactorily. This is that in some cases the nervous substance of mice dead of experimental tetanus is found to be toxic for other mice, the mice dying with paralytic symptoms. I have observed also that the point of infection is not a matter of indifference as regards the development of tetanus; for example, the subdural injection acts more quickly and more virulently than the subcutaneous.

The Mode of Action of the Tetanus Toxin.

Rosenberg and Gumprecht consider the cause of the tetanic symptoms to be an increased reflex irritability of the spinal cord; Rose thinks that it is a forced contraction of the muscles emanating from the brain. Undoubtedly tetanus is a disease the poison of which acts primarily on the nervous system, and the rigidity which begins at the point of inoculation indicates an irritability of the reflex currents, which lead from the injection point through the protoneuron to the spinal cord and thence through the centripetal neuron to the muscles of the same region. Certain investigators (Nissl, Marinescu, and myself) have found changes in tetanus in the cells of the anterior horns and in certain commissural cells, especially degeneration of the axis-cylinder processes and the Nissl elements, with increasing homogeneity of the basement substance. Goldscheider and Flatau recognized especially in the incubation stage of tetanus chromatolysis and also swelling of the nucleolus, which recedes as soon as tetanus appears. Besides these changes there is always hyperæmia in the central nervous system, especially in the motor centres; we also find here often small hemorrhages. These changes are usually in human beings more pronounced in the brain than in the spinal cord. Tetanus appears in man, as previously stated, in various forms, but rarely as a vaccination tetanus with special affection of the extremity near tho wound. We shall return to this later. The symptoms in horses are also singular and similar to those in human beings. I would mention here especially the peculiar course of the fever which usually exists at the beginning of the disease in acute cases; in protracted cases it is often temporarily absent, but the temperature rises again towards the end of the attack, and increases during the agony and after death. Agonal temperatures of 44° to 45° C. (111.2° to 113° F.) which increase after death to 46° (114.8° F.) are not very rare. In many cases there is, however, no increased temperature after death.

Pathological Anatomy.

In post-mortem examination of tetanus cases we find few positive lesions. First of all we have to examine carefully whether there are any small wounds, injuries, scars, or penetrating foreign bodies, especially in the extremities or under the nails. In many cases these are discovered only post mortem. We often find here a small collection of pus, often surrounded in the depth by hyperæmic or hemorrhagic tissue. In the midst of these we often find a splinter which has produced the tetanus. In acute cases the brain is heavy and dense; the gray substance is hyperæmic; in older cases the meninges are often more moist, the brain is softer and œdematous, in the ventricles are greater quantities of fluid, and there are sometimes small hemorrhages. The anterior horns of the spinal cord are usually injected and are often softer; the bronchi are frequently the seat of catarrhal inflammation, the lungs are often œdematous, and in older cases in a state of splenization inferiorly and posteriorly. The abdominal organs are usually hyperæmic; in older cases we find beginning parenchymatous degeneration of the heart and kidneys. Not rarely there are hemorrhages in the neighborhood of the spinal ganglia and in the pericardium. The muscles usually do not show anything special; the nerves which lead from the point of infection are sometimes thickened and hyperæmic; here and there we find nodular thickenings.

As a rule, we may say that the macroscopical findings are mostly due to secondary changes.

Pathogenesis of Tetanus in Man.

It is certain that human tetanus may originate from various causes; usually the cause is the penetrating of a tetanus bacillus or a toxin-containing substance; in other cases this cannot be demonstrated, and for this reason some authors assume that in these cases the disease cannot be due to the effect of a tetanus bacillus or its toxins.

Let us first consider those cases which are generally designated as traumatic tetanus. These may be divided into (1) cases produced by penetration of infectious splinters, probably the most common cause; (2) those arising from wounds not kept clean; (3) tetanus gangrenosus; (4) inflammatory tetanus; (5) putrid tetanus; (6) tetanus produced by castration; (7) that following operations, among which may be included (8) tetanus of the new-born, and (9) puerperal tetanus. In regard to the first, produced by *penetration of foreign bodies* of all kinds, splinters, nails, bullets, etc., we must say that most of these accidents do not result in tetanus, even if the bodies are dirty or mixed with excrement or earth. Foreign bodies which enter without causing special inflammatory reaction and without exciting suppuration may, as is well known, be carried in the body for years without harm. Organic bodies produce usually more irritation and the wound does not so readily close over them. Foreign bodies are especially dangerous (and particles of dirt the same) if they penetrate deeply and if the wounds are then closed without their being removed. It may happen, especially in extensive injuries produced by great violence, that fragments of infectious matter penetrate the tissues deeply and are overlooked when the wounds are cleaned.

I have seen cases in which tetanus broke out one month after such an injury when the wound had nearly closed, but when pus had formed in the depth of the wound and around it. In other cases infectious material was left behind after amputations. It occurs especially often that tetanus breaks out during the treatment of an apparently clean wound, and foreign bodies like particles of earth or manure are not discovered until the autopsy is made. In such cases we find that inoculation with these substances or with the pus will produce tetanus in animals. The appearance of the diseased part from which the tetanus originates is generally very peculiar. There is usually dirty pus present and often a gangrenous odor is perceptible. The focus is as a rule not sharply marked and it is surrounded by an area of œdema, often containing blood. The neighboring lymphatic glands are apt to be œdematous, and inoculation from them often produced tetanus in one of my cases. It is proved beyond doubt and especially by my numerous cultures that this centre contains various bacteria, among which may be mentioned a saprogenous and gas-forming kind of coli communis, one like proteus vulgaris, the staphylococcus aureus, and also in one case a not very virulent bacillus resembling the hay bacillus.

These bacilli are certainly responsible for the formation of pus and their action surely prepares the soil for the tetanus bacillus. It probably develops from a few spores, which increase and produce toxins, and these finally cause tetanus.

This explanation of tetanus is rendered the more probable by the frequency with which the disease occurs in case of gangrenous wounds, in which, however, there are probably also infectious foreign bodies to be found.

But we know of a series of cases in which gangrene was not the result of the penetration of any foreign bodies, nor even of loss of tissue. In these cases we must suppose that the gangrene was produced by bacteria which could easily penetrate the injured parts. It is plain that the tetanus spores which are so widely distributed may penetrate at the same time and, with the cooperation of other bacteria, produce tetanus. I have succeeded in producing tetanus by a small piece of the gangrenous part of the lower extremity of a man, who was bruised by being run over, without any loss of substance and who died ten days after with violent symptoms of tetanus.

Gangrenous foci, especially those beneath the surface, form favorable conditions for culture of the tetanus bacillus, because gangrene favors the anaerobic growth of the bacillus and furnishes material for its culture. Thus it is plain that even superficial gangrene may lead to tetanus; while usually only deep, obliquely penetrating or closed wounds produce the disease.

In these cases there is frequently simple inflammation with putrefaction. But often the wound shows peculiar changes before tetanus occurs; the parts begin to swell and are diffusely red, sometimes ecchymotic, and severe pain radiates from the wound, or even convulsions may ensue. According to Larrey the following symptoms precede tetanus: Restlessness, malaise, a drying up of the suppurative process, reddening, marbled discoloration and drying of the granulations, pains along the nerves and blood-vessels of the injured region, convulsions, and carphologia; but Rose regards these symptoms as unconnected with tetanus, and insists that the disease occurs suddenly without any prodromes. It is not astonishing that this inflammatory form of tetanus is associated usually with injuries of bones and joints, because deep inflammation with suppuration is the rule in such cases, and they offer favorable conditions to the growth of the bacillus. The tetanus of ulcers is interesting because it shows that a superficial, neglected ulcer may serve as a point of entrance for the tetanus bacillus, which does not pass through a clean and carefully disinfected granulating surface of an ulcer due to overlooked foreign bodies in the depth.

If the ulcers resulting from pressure or erosion (ulcers of the lower part of the leg) or the breaking down of neoplasms become ichorous or superficially gangrenous, then they may become the portal of entrance of tetanus infection.

Tetanus septicus arises from deep ichorous foci which create at the same time sepsis and progressive destruction of tissues and formation of gangrene, fistula, and erosion of lymphatics and blood-vessels. In such cases the bacillus may penetrate deeply at the beginning or later, this being made easier by the destruction of tissue.

Tetanus may also appear in seemingly clean granulating wounds, especially after the extirpation of large tumors, if the surface of the wound is very large, if the granulations are of long duration, and if shreds of the tumor tissue are being gradually destroyed. In such cases the wound, open such a long time, gives opportunity for the penetration and growth of the bacillus.

Tetanus after operations has become rare since the development of asepsis and antisepsis, yet it sometimes occurs, especially after operations in which many ligatures are tied and in which a pedicle is left open whereby opportunity for infection is furnished; or after the extirpation of tumors which had ruptured or which were purulent or gangrenous, as especially in operations on the breast.

If we consider that the tetanus spores resist our ordinary sterilizations, we shall be astonished at the rarity of tetanus following operations; but we know on the other hand that the tetanus spores are hardly able alone to produce tetanus but that there is required at the same time a weakening of the tissues, especially by pus bacteria, and that these are destroyed by our antiseptic measures. Formerly it was believed that tetanus, especially that form occurring after castration, hernia operations, or ovariotomies, was due to the many ligatures and especially to the injury to the nerves caused by them; we now know, however, that it is due in such cases to an infiltration of the wound, especially of the pedicle. In the many cases of tetanus in horses after castration it has been demonstrated that the disease is due to an infection of the caissons which are applied to the seminal cord and under which it is cut. If the horses are removed shortly after the operation, and the wound comes in contact with all kinds of infectious material like earth or manure, it is very natural that the susceptible animals should be attacked by tetanus. Moreover, tetanus bacilli have been found on the caissons themselves. If, however, the caissons and the wound are carefully cleaned and the horses are kept quiet after the operation, then tetanus after castration is rare. But there are exceptions in the case of stables which contain such virulent bacilli that it is hard to avoid them. In such stables the slightest wounds will lead to tetanus. Contamination of the wounds with fæces is another very common cause of tetanus; but in wounds, either operative or traumatic, of the perineum, anus, and neighboring parts this is hard to avoid.

I was the first who produced tetanus by infection with fæces of human beings (*Centralblatt für Bacteriologie*, 1890). This was after Sormani's experiments had proven the possibility of the bacillus penetrating the alimentary canal. This explains why hernia operations are so often followed by tetanus.

Generally tetanus is more frequent in men than in women, as men are oftener exposed to injuries; but *puerpereal tetanus* is not even very frequent in women, and even tetanus in pregnant women does not always depend upon their pregnant condition. Abortion complicating tetanus may be due to some other causes. The real puerperal tetanus is produced after abortion or delivery by infection of the placental wound or of some other injury inflicted during delivery. In aseptic or antiseptic midwifery tetanus is rare; but where no such measures are taken, it is very frequent—as in Bombay, where two hundred and thirty-two cases were reported in three years (Playfair), on the Senegal, etc. An operation such as forceps delivery, or the introduction of a tampon made of non-sterilized material, is another cause. So also are artificially produced abortion, especially by the introduction of foreign bodies, and the retention of placental remnants and their removal.

It is singular that in this form tetanus often appears very late; and often also in cases in which no manual interference had occurred. This has led many authors to suppose a different etiology for these cases, but the late appearance of tetanus can be easily explained by the peculiar characteristics of the tetanus bacillus; and direct infection is often replaced by autoinfection, especially by bacilli from the intestinal contents.

Tetanus of the new-born is easily explained by the presence of umbilical wounds in which Peiper, Papievsky, and myself found numerous bacilli even when there was little inflammation or suppuration. When wounds of this region began to be carefully and antiseptically treated, this form of tetanus became very rare. In Berlin in 1871 in every 1,000 births there were 12.5 cases of tetanus, but in 1890 there were only 2.69 tetanus cases to 1,000 births.

Tetanus from internal causes constitutes a connecting link between the forms we have just been considering and those occurring without open wound—the so-called idiopathic tetanus.

Cases of tetanus from injuries of the tongue, dental operations, injuries of the pharynx, diphtheria, and tonsillar abscesses, are not rare and may be especially induced by the penetration of foreign bodies, scraping off of diseased tissue, gangrene, and suppuration—just as in tetanus produced by external causes. The behavior in this respect of the deeper mucous membranes, especially that of the alimentary tract, is not so clear. We should suppose that the various forms of ulceration of the œsophagus, stomach, and intestines would facilitate the entrance of the tetanus bacillus, the more because it is not rarely found in the food and excrementitious matters. But we know of cases occurring after typhoid fever which may be explained by absorption through the fresh or cleaned ulcers. It also seems that the diseased bronchial mucous membrane is disposed to invasion by the tetanus bacillus, and some cases of rheumatic tetanus may be explained by this mode of entrance of the bacillus.

Scar tetanus, in which the disease originates from an old cicatrix, is to be explained by the supposition that old tetanus spores were left in the scars, and revived at a given moment and were carried by leucocytes into a part beneath the surface where favorable conditions existed for the manufacture of toxin (suppuration, gangrene, necrosis of tissue, hemorrhages, etc.).

Idiopathic Tetanus.—We know that tetanus may be produced by the passage of toxin through the skin into the subcutaneous tissue, whence it is readily taken up into the circulation, but cases of tetanus are met with in which there has been no opportunity for the entrance of bacilli or of the toxin into the subcutaneous tissues. To these cases belong tetanus in simple fractures and luxations, and in furunculosis, scar tetanus, tetanus following concussion of the brain or any severe blow on the head, and rheumatic tetanus.

Cases were known in ancient times in which fractures or luxations without external injury were followed by tetanus; Wilnos, Larrey, Plenk, Travers, Busch, Fornet, Langenbeck, and others have reported cases in which simple or complicated fractures resulted in tetanus, sometimes even after they were healed. The question is whether in these cases tetanus bacilli or spores may not have penetrated the skin, which may on the occasion of the accident have been abraded, or whether the specific microbes came from the earth with which the injured part must have come in contact, or whether there may have been tetanus spores somewhere on the skin or mucous membrane which found occasion to produce tetanus after their culture in a remote part by inflammation or loss of substance. I would draw especial attention to the bronchial catarrh which is usually present in such cases, and also to the assertion of Carbone and Ferrari, who found attenuated tetanus bacilli in the inflamed bronchi. Perhaps there were small skin abrasions which were overlooked, through which spores may have penetrated which afterwards slowly developed in the deeper tissues. It must be assumed that tetanus spores may emigrate from a latent focus to the injured part, perhaps, as Vaillard, Vincent, and Rouget assert, from scars and enclosed in leucocytes, which assumption is supported by the observation of Rudinger and Schnitzler, who demonstrated the presence of tetanus bacilli and toxin in the swollen lymphatic glands nearest the inoculation wound.

The fact that tetanus bacilli usually are destroyed ten hours after inoculation does not apply to these cases, as it applies only to normal tissue, while we know that the tetanus spores in an enclosed focus may exist for weeks, and even for months, if foreign bodies are present. Cases of tetanus from widely diffused boils and following contusions or falls are not rare, but there are in most such cases contemporary abrasions of the skin, even if superficial, or gangrenous, or necrotic shreds which we know may favor the lodgment and increase of tetanus spores. In other cases the furuncles become purulent or gangrenous, so that infection easily occurs.

Finally tetanus has developed in many cases after the opening of a purulent or necrotic hæmatoma, so that we may assume in these cases a secondary infection. Some cases in which slight injuries were said to have been inflicted, without, however, any solution of continuity, appear to me not sufficiently demonstrated. In regard to scar tetanus, of which we have spoken before, we may add that such cases are probably due to the presence of embedded foreign bodies (as in a case of Dupuytren) or to tissue containing tetanus spores. The influence of irritation or stretching of the nerves cannot, however, be denied in such cases. The participation of the nerves appears to be true in tetanus as well as in rabies. But the nervous tissue is not essential to the formation of tetanus toxin as it is to that of the rabic toxin. The fact that the tetanus virus is localized in the nervous system raises the presumption that nervous irritation makes it more sensitive. There are several cases on record of tetanus starting from scars in the parts about the nails, but probably this can be explained by the presence of tetanus spores in the dirt under the nails, and these spores might easily have entered at the time of injury. In my experiments, however, I was able only once to cause tetanus by inoculation with the scrapings from under the nails of patients with the disease. Although in these cases the participation of the tetanus bacillus cannot be denied, various observations indicate the prominent rôle of irritation and stretching of the nerves. This is also confirmed by the result of resection of the nerves in this form of tetanus and even if we assume the presence of tetanus spores in the nerves, we can but recognize that their effect is even more localized here than in other places.

The occurrence of tetanus after *blows on the head and neck* and *concussion of the brain* also indicates the importance of irritation of the nervous system. Those very rare cases in which there is no injury at all and in which tetanus or at least some of its symptoms appear immediately or a few hours after the insult, are probably due to direct violence causing irritation of those parts of the central nervous system which produce tetanus symptoms; just as experimental blows and concussions of the nervous centres in animals produce tetanus or epilepsy. But all these cases do not prove anything against the theory that tetanus is produced principally by tetanus toxin, although we cannot deny that some cases of tetanus cannot readily be traced to infection.

Especially interesting in this connection are the cases of *rheumatic* or *idiopathic tetanus*, or tetanus a frigore. These cases are especially mentioned by Rose as characterized by the quick appearance of tetanus (a few hours after the exposure to cold), which fact can surely not be connected with infection or poisoning.

In all these not very rare cases we observe as a common symptom great fatigue with profuse perspiration, succeeded by a general catarrh, and followed after a few hours by pains in the back, trismus, and more or less pronounced tetanus.

The prognosis in these cases is a little more favorable than in traumatic tetanus, but there are also very virulent cases among them. In some of these cases tetanus toxins have been looked for in vain in the urine and in the blood. Another form of rheumatic tetanus is that in which tetanus follows other rheumatic ailments, like inflammatory rheumatism, catarrh, rheumatic diarrhœa, pleurisy and pneumonia, and rheumatic nephritis. Here we must, however, assume the association of bacteria, while in the previous cases several hypotheses are possible. Rose, for example, supposes that the bacteria of rheumatism may occasionally enter the brain, like those of tetanus; while Carbone and Perrero hold that attenuated tetanus bacilli might in such cases be absorbed from the bronchial mucous membrane. I myself believe that we may in tetanus, as well as in other bacterial diseases, assume the existence of concealed portals of entrance besides the usual and evident ones. Especially, it seems to me, that the bacillus may grow exuberantly in the crypts of the tonsils, in hollow teeth, in certain parts of the intestines, under certain favorable conditions excited by the action of cold, and that they may thus give rise to the symptoms of tetanus.

The great number of tetanus spores everywhere about us and even in the human body and, as I have demonstrated, in the fæces, surely indicates such a probability. It would be premature to hold other causes besides tetanus toxins responsible for rheumatic tetanus until further very careful experiments in this direction have been made. It is certainly reasonable to consider irritations of nervous tissue, concussion of the brain, colds, and catarrhal diseases, as favoring causes, at least so far as they are able to make small quantities of tetanus toxin more effective. The experiments of Roux have demonstrated how much certain weakened conditions of the organism render it more susceptible to the action of toxins. Thus it is especially the so-called rheumatic type of traumatic tetanus (Rose) which shows how easily tetanus is produced by changes of temperature, suppression of perspiration, and living in dirty and damp apartments. But here we must not forget to be critical; for example, tetanus in Cayenne is much more frequent on the seashore than in remote forest regions, but this must not be ascribed to the action of sea air, but to the well-known tetanogenous action of the soil near the shore. Similarly the frequency of tetanus of the new-born among the negroes in tropical America should not be ascribed to the exposure of their cabins, or to the changes of temperature, but to the besmearing of the umbilical cord with infected earth. The aborigines, however, cover the umbilicus with a plaster, and consequently their children do not die from this form of tetanus. Unfortunately it is not yet decided whether dust may contribute, and how much, to the production of tetanus. Dust undoubtedly frequently contains tetanus spores which may drop on wounds, and on such parts as may allow their increase and formation of toxins. But the cases are rare in which this explanation is admissible, since there is usually a contamination of the wound with earth or other matter containing the pathogenic agent in traumatic tetanus. But in hospital epidemics of tetanus this explanation may be necessary, although even there contamination of the wounds cannot be absolutely excluded. If, for example, a patient with traumatic tetanus enters a surgical clinic, he will be examined, and as much as possible all tetanus material will be removed, and then other cases are examined. Of course this is done only after previous cleansing and sterilization of hands and instruments, but this sterilization is usually not directed against tetanus spores, which are not killed by simple boiling or by our ordinary antiseptic solutions, and hence we may transfer these tetanus spores by means of the hands and instruments from one wound to the other. This method of transfer seems to me much more plausible than that by means of the atmosphere, or of dust. To be sure, there are cases reported of patients who acquired tetanus after lying in a bed where persons suffering from this disease had been before, and the epidemic has not ceased until the beds were removed to a place less exposed to draught; and these cases are said to be due to the draught and to the dust carried by the wind. But these observations are so rare and so imperfect that they cannot be relied upon. Certainly there is no case known which can be positively traced to the action of cold or to infection by dust. However, we do not even need to invoke the action of cold in the production of tetanus without apparent entrance of a bacillus, because idiopathic forms occur in which no trace of a cold has existed.

In concluding this section I desire to add a few words concerning the discussion as to the "unity" or "duality" of tetanus. While Verneuil insists that there is really only one kind of tetanus, produced by the tetanus toxins, others, like Rose, believe in a form of tetanus which is not produced by the toxin of the tetanus bacillus. Verneuil explains the occurrence of tetanus without any evident point of entrance of the toxin by the inhalation of the tetanus spores or their absorption through the normal skin. Rose believes that in such cases other spores, especially those of other internal diseases, or any of the poisonous products of metabolism may cause the disease. "Rheumatic tetanus" he believes to be due to the action of some other virus.

While such an hypothesis may be admissible in the case of many diseases which may be caused by various bacteria, I believe that it is inapplicable in the case of a disease with such typical symptoms which can be produced experimentally by the tetanus bacillus alone. We are certainly not justified in ignoring positive facts, even though they are not wholly elucidative, in order to plunge into the chaos of pure hypothesis.

Symptoms.

Experimentally produced tetanus in animals, such as we have described, has an absolutely typical course. In mice we see, one or several days after inoculation with the tetanus germs, an attack of true experimental tetanus; in cases of inoculation with toxin it appears quicker than when the bacilli are injected; in inoculation with destruction of tissue at the same time the disease occurs even more quickly and surely than after introduction of pure cultures; this tetanus begins near the place of infection, spreads to the other side, ascends and ends in tonic and clonic convulsions and death. In some animals, as, for example, cats, tetanus, as my experiments show, frequently becomes chronic and heals spontaneously; in warmed frogs it begins from four to six days after the infection and principally on the anterior extremities (Babes, Pascariu). In horses the course of the disease is about the same as in human beings. There is always a stage of incubation of at least eight hours.

In man tetanus occurs as the result of an injury or without an injury. The course of the disease in either case is the same, but it is nevertheless necessary to study the symptoms of the two separately. There are also cases in which the first symptoms appear soon after the injury—within twenty-four hours; others in which several days elapse without any symptoms; and finally cases which appear weeks or even months after the injury. Rose first pointed out that tetanus has a tendency to go through several stages, more or less pronounced, but that death or recovery often interferes with the development of several of these stages.

The first stage in human beings is always trismus, although, especially in rheumatic tetanus, we may observe other symptoms first, as for example pharyngeal catarrh, pains in the back, and sometimes rigidity of the extremities or of the neck. I am disposed to consider these symptoms, like the neuritic pains extending from the wound, as not absolutely coincidental or belonging to complicating ailments, but I must admit that they are usually absent in the typical forms of tetanus. If the first stage is not very pronounced and ends in recovery, we call it a slight or incomplete tetanus. We distinguish cases in which trismus appears on the first day from those in which it remains incomplete for several days. We further meet with cases, in animal experiments as well as in man, which are quickly fatal, others with chronic course, others ending in the first stage, in the second stage of opisthothonos, in the stage of clonic convulsions, or in collapse.

Acute, Grave Cases.

Trismus appears usually without any premonitory symptoms. The injured man suddenly observes that he can hardly open the mouth, or not at all. There exists a tonic spasm, an involuntary permanent contraction of the muscles of mastication. Tetanic trismus is distinguished from trismus from other causes by participation of the masseters of both sides, and by their anterior border being clearly felt through the cheek; further, according to Rose, by the participation of the muscles of the neck, so that the patient can hardly touch the chest with his chin. To recognize the trismus, this first infallible symptom of tetanus, we must first convince ourselves that there is no inflammation or tumor in the mouth; then we examine between the teeth and the cheek to feel the sharp border of the tetanized masseter muscles; finally we take firm hold of the patient's neck to convince ourselves of rigidity or of the presence or absence of pain. Frequently we observe a singular, staring, smiling facial expression (risus sardonicus) or a contraction of the orbicularis oris muscle, causing a protruding of the lips. These voluntary contractions or movements, however, are not essential and can be easily suppressed; but the trismus increases constantly and the teeth remain finally firmly pressed together, and both masseter muscles can be felt like two tightly drawn strings or cords. Often on the first day, in slower cases after several days, we note rigidity and tonic contractions of the muscles of the neck (opisthotonos), a sign of increasing gravity of the disease. In cases of incomplete trismus the patients may make a joke of their condition, but there is nothing of this kind in the fully developed disease, and the gravity of the state is made apparent by the difficulty of nutrition resulting from the firm lockjaw, and by the pressure on the larynx due to beginning rigidity of the neck, which forces the larynx forwards and draws the head backwards.

In all cases the anterior abdominal muscles, especially the two recti abdominales, are rigid. Frequently that whole region appears like a hard plate which makes the patients suffer from precordial distress, gastralgia, and difficulty in micturition. Often these patients cannot urinate voluntarily at all. There is also difficulty emptying the rectum. In grave cases all these symptoms exist as early as the first day. The rigidity increases steadily, and extends especially from the neck to the back so that the patient is stretched stiff with the trunk arching with concavity backwards.

Such cases end almost always fatally. Other cases, in which trismus is moderate, in which the cervical and abdominal rigidity hardly exists, in which the patient may open the mouth several centimetres, and in which the occiput remains away from the back and the chin can be approximated to the chest, are to be considered slight attacks in which recovery usually takes place. But even cases in which opisthotonos is very severe, so that the occiput touches the back constantly, may end in recovery.

Opisthotonos has also various degrees. In some cases, after slight injuries, the patients follow their ordinary pursuits for several days in spite of some difficulty in walking and eating. They hold their body forwards and so maintain their equilibrium, but they have a queer sensation, the back is stiff and hard. Usually the muscles of the pelvis and of the lower extremities are free.

In opisthotonos the trunk and head as also the thighs are forcibly bent backwards, the muscles being hard and stiff, so that the trunk forms a rigid arch. Sometimes even the knees and ankles participate in this condition, and it is said that in such cases the heels may even touch the head, so that the body forms a circle.

We see from this account that the rigidity in tetanus follows a regular and definite course in animals and men, with this exception: that in experimentally induced tetanus in animals the first symptoms appear near the wound, while in man the first manifestation is trismus. The cause of this is difficult to find. The tetanus toxin attacks in the test animals first the cells of the anterior horns of the affected part of the cord and produces convulsions starting from there. Nissl, Goldscheider and Flatau, Marinescu, and myself have observed peculiar changes in the the cells of the anterior horns of the spinal cord in animals, while I could not find similar changes in the same cells in man as in horses. But if we consider that the changes in the cells, according to Goldscheider and Flatau, recede as the rigidity becomes complete, we must regard these changes more or less chance sequelæ of the real changes in the cells and therefore as not very important. The beginning of tetanus in experiment animals seems to indicate that the toxin first attacks the motor cells of the irritated parts of the central nervous system and begins to operate from there.

In man the place of infection probably causes an irritation of the corresponding part of the spinal cord also; but here the specific irritability of the centre for the masticatory muscles prevails, just as in frogs the anterior extremities are first attacked. In horses tetanus usually attacks principally the neck, ears, and jaw, soon the whole body and very characteristically the tail, which is erect and points upwards. In pigeons opisthotonos and trismus are the rule, but there is also a peculiar wheel-like appearance of the tail. These variations may be explained by the different degrees of sensitiveness or reaction to the specific poison of the various motor centres in animals.

We find an analogous condition in rabies, in which undoubtedly the irritation proceeds from the bite, as does also the gradually ascending infection. We also find in hydrophobia irritation of the corresponding nerve leading from the seat of injury and pronounced inflammation at the point where it enters the cord. Nevertheless the disease manifests itself first by symptoms which indicate the affection of the same nerve centre as that which seems specifically sensitive to the action of the rabic virus.

The further extension of tetanus symptoms depends primarily on the specific irritability of the various motor centres, and also on the gradual and regular extension of the rigidity downwards.

A later stage of the disease is that of muscular spasms which are, according to Rose, primarily not reflex. We often see in advanced stages an increase of the muscular rigidity with spasms and opisthotonos as also violent trismus. These contractions can be produced by a touch in animals, and are therefore of a reflex character; but in man Rose could not produce them voluntarily. These spasms occur suddenly, at frequent or infrequent intervals—often several times in a day, sometimes a few only during the course of the sickness. In mild attacks the patient simply starts; in more severe ones a violent contraction comes on suddenly and extends from one part to another of the body; dyspnœa increases, the pulse is accelerated, and perspiration breaks out. The patient may remain for several hours in this condition. The most violent spasms which lead to very marked opisthotonos, cyanosis, and threatening apnœa, often end fatally.

Most patients die during one of these attacks, even after apparent improvement has occurred.

According to Rose the reflex tracts are involved but gradually in man. Then we see, usually as a result of external irritation, tonic convulsions lasting several minutes, similar to those described above. But these reflex symptoms are much less pronounced in tetanus than in strychnine poisoning or in rabies. We occasionally observe reflex convulsions, the same as in rabies, during eating or drinking, probably a result of difficulty in swallowing; in other cases change of position, pressure, or shaking excites an attack. The frequent recurrence of the attacks probably increases their violence. In the intervals between the most violent attacks we see the patients frequently in good spirits, their sensorium is unaffected, and the action of the mind is perfect. In artificially produced sleep the rigidity ceases, to reappear on awakening. The disease may, however, be very grave and still admit of recovery; rigidity lessens gradually, the jawbones can slowly be opened, the spasms become rarer and weaker, and finally the rigidity disappears entirely with occasional slight relapses.

The rigidity of the muscles, the fatigue, the inanition, and the insomnia quickly reduce the strength of the patients, and sooner or later, sometimes from the beginning, exhaustion comes on. In such case the trismus usually relaxes, but heart failure frequently causes sudden death. Robust persons resist longer, the weak and debilitated succumb rapidly.

Rose, who describes collapse as the fifth stage of the disease and very accurately, lays especial stress on the sudden, unexpected relaxation of the trismus with pendent jaw, the unimpaired sensorium, the sudden rise of temperature above 40° C. (104° F.) and the accelerated pulse becoming gradually filiform; he regards all these symptoms as very grave, presaging death within a few hours, from the force of the convulsions, asphyxia, œdema of the lungs, or paralysis of the heart.

Sometimes peculiar spasmodic contractions of the arms are observed before and after death. Frequently we note bronchitis, bronchopneumonia, more often hypostatic congestion of the lungs or pneumonia, and also albuminuria in the last stage of the disease. At the autopsy we often find old lesions of the kidneys, and when these changes exist there may be uræmic symptoms, especially in the last stage of the disease. In the subjects of chronic alcoholism delirium is a frequent symptom.

CHRONIC AND INCOMPLETE FORMS.

If trismus is fully developed within twenty-four hours there is hardly any chance for recovery. But if it gradually increases during several days, the outlook is more favorable. In these cases the other symptoms develop more slowly also, and it sometimes takes one or two weeks for the disease to mature fully. Death sometimes results from the convulsions or collapse in these chronic cases, but the more usual termination is in recovery at any stage of the disease.

Recovery is the most frequent termination in the incomplete forms of tetanus. Here trismus hardly becomes complete, and the prognosis is the more favorable in proportion to the distance which the patients may separate their jaws. If we can introduce one or two fingers into the mouth the case is a light one, and it is the more grave the narrower is this interval. But even in the first case we have to be very careful in our forecast, because trismus may become very severe after the lapse of a few days and more violent spasms may then occur. Mild cases of tetanus are doubtless often overlooked or the disease may be mistaken for a pharyngeal catarrh. But if, as a result of some irritation, or an operation, or an injury, reflex spasm appears, then the disease will be recognized. It cannot be doubted, however, that slight cases often end in recovery without being recognized as such. The person is slightly troubled in eating and drinking, he cannot put forward his tongue fully, he suffers from insomnia and also from some rigidity of the neck, back, or extremities, but is not prevented from pursuing his usual avocation. As these cases may suddenly get worse, it is highly important—especially as we possess in the antitetanic serum a remedy which is of great value in such cases if applied early—to examine all such cases carefully and establish a correct diagnosis.

Varieties.

The above-described symptoms are the same in all forms of tetanus in man, but are especially pronounced in traumatic tetanus. They are usually more pronounced when there are extensive, especially gangrenous wounds, and their course is more rapid than in cases of slight injuries. Generally tetanus is the more dangerous the deeper and more extensive the injuries are; but even slight injuries sometimes end fatally. Certain varieties of tetanus require special notice, for the reason that in them there are other symptoms present besides the usual ones.

Tetanus of the new-born, which usually occurs a few days after birth, is modified by the tenderness of the organs in infancy, and by the method of obtaining nourishment. We have to distinguish here early cases (four to six days after birth) and later ones, coming on eight or ten days after birth, perhaps at the time when the stump of the umbilical cord falls off; this may be regarded as scar tetanus.

In all cases trismus is the most conspicuous symptom, so that the disease is often called trismus neonatorum. As a result of this the babies cannot nurse or cry and they die usually within forty-eight hours, opisthotonos having already appeared. We also see spasms and tonic convulsions in such cases. The disease is often not recognized, especially if attention is not drawn to the rigidity of the masseters. In cases which develop later there are spasms at long intervals, between which the symptoms are slight, except that the babies do not nurse. The symptoms vary greatly according to the age of the patient. In children there is sometimes hardly any trismus; the disease frequently becomes chronic, but after a longer or shorter duration it usually ends fatally. Tetanus is also observed in old people, though not so frequently as in those of middle age.

Tetanus puerperalis is another special form. It is not very frequent, and even in women tetanus from other causes is more common.

Abortion is often a result of tetanus, and such cases must not be confounded with puerperal tetanus. This is the result of an infection of the uterine wound. Tetanus occurring after abortion is caused by a similar injury. We find such cases with special frequency among uncivilized races. Thus numerous cases have been described as occurring among the native population in Bombay and elsewhere in India. In these cases as well as in abortion tetanus infection may be introduced during a slight operation, or in consequence of manipulation of some sort. But even in the absence of such injuries, and even if the womb is found in involution, we must believe that the specific poison has entered through some lesion of the womb, because even if no foreign body can be found, we cannot exclude the possibility of autoinfection in the presence of such a large denuded surface. We hear of cases in which the symptoms of tetanus came on when the woman left the bed from four to six days after delivery, and we are often told in such a case that she was exposed to a cold immediately before trismus occurred. The symptoms of this form run the same course as those of the other varieties of tetanus.

The *facial tetanus* of Rose is a variety of tetanus which sometimes follows injuries in the region of the facial nerve, and is occasionally accompanied by paralysis of this nerve. This variety is not common, for while eighty per cent. of all cases of tetanus are the result of lesions in the extremities, and about ten per cent. of wounds of the trunk, only five per cent. are due to face injuries. Cases of tetanus following wounds of the head are generally very rare—and there is a difference between wounds producing ordinary tetanus and those producing Rose's facial tetanus.

Facial tetanus comes on a few days after some very trivial injury in the region of the facial nerve; in the face, ears, lower jaw, temples, muscles of the occiput, while the patient at the same time suffers from trismus and paralysis of the facial nerve usually in its whole extent; sometimes only partially. In some cases the patient can yet whistle, but his face shows some distortion and there is inability to close the eye completely on the affected side. In other cases there is complete facial paralysis with drawing of the face to the sound side, and there is inability to whistle, to blow out the cheeks, or to elevate the alæ nasi. At the same time there is usually incomplete trismus with opisthotonos following; rigidity of the abdomen and back is usually slight; but dysphagia is marked and there are also spasms in the throat during efforts to eat. These symptoms are often so pronounced, while the opisthotonos is not severe enough to explain them, that I cannot consider them as a mechanical result of the same. In considering their analogy to the deglutition spasms in rabies, I am convinced that they are due to a special central reflex spasm of the muscles of deglutition. There are, however, cases of facial tetanus without glottid spasms, and though there is in such cases simply rigidity of the head and neck, though the urine and fæces are controlled, and there are no spasms, this form is still very dangerous, because inanition occurs often quite rapidly.

Some cases remind us of those cases of rabies in which, after apparent improvement and without any especial symptoms, sudden death occurs. In the chronic and incomplete cases recovery is very slow, with trismus occasionally returning and facial paralysis remaining for a considerable time. Undoubtedly in such cases the trauma combined with the irritation of the specific tetanus poison has injured the facial nerve, while the tetanus toxin penetrates the brain in the usual way and affects the nerve centres of the medulla oblongata, especially those for swallowing, just as does the toxin of rabies.

Rose explains the paralysis of the facialis by assuming a slight ascending neuritis of this nerve, but without being able to prove it. Neuritis of the facialis may easily produce paralysis by pressure because the nerve passes through a narrow bony canal. The electrical irritability is preserved in the paralyzed facial nerve, and we observe no symptoms of degeneration. Paralysis in other forms of tetanus is mentioned by some, but its occurrence has not been proven.

Kitasato speaks of paralysis in man in cases in which he injected small quantities of tetanus toxin into the femoral vein. I myself could never produce a similar paralysis in spite of numerous experiments, and I believe that the paralysis in such cases might have been due to an injury to the nerve on the occasion of the injection. It is not proven that the tetanus bacillus or its toxin produces any paralysis. Certain spasmodic contractions of the injured side of the head in tetanus of the head must not be confounded with cases of paralysis of the facialis in which the contraction is on the sound side.

Sometimes virulent bacilli have been found in the wound in cases of facial tetanus as well as in other cases of traumatic tetanus.

The symptoms of the so-called *idiopathic tetanus* are the same as those of traumatic tetanus. We have seen especially in rheumatic tetanus that the alleged etiological action of cold and the sudden onset of the symptoms, often at the same time with other rheumatic disturbances, are somewhat peculiar. The prognosis is a little better than in traumatic tetanus, but not quite so good as in facial tetanus. The symptoms in this form are at first not always symmetrical. They further seem to be connected somewhat with muscular rheumatism, occurring at the same time with these, and they also appear to be severer in these rheumatic parts. This may easily be explained by the fact that tetanus has a tendency, slight it is true, to affect the weakened portions of the body a little more severely. We also know by experiment that animals which have been weakened before the injection by some other infection are more susceptible to the tetanus poison than healthy animals. Tetanus bacilli are not found in such cases, which is natural when we remember that their point of entry is unknown. I would in such cases examine especially the tonsils, the nose, the bronchi, the contents of intestines, and even dirt from the surface of the body. It is known that in some cases the removal of scabs from the nostrils has arrested the symptoms.

While we must be careful in such cases not to consider harmless bacilli from bronchi or intestines as attenuated or aerobic tetanus bacilli, we must, on the other hand, not be too ready to assert that rheumatic tetanus is not dependent upon tetanus bacilli. Some authors even go so far as to hold that when wounded persons are exposed to unfavorable climatic conditions, and suffer from rheumatism, the resulting tetanus is due to the action not of tetanus bacilli but of some rheumatic virus. The occurrence of tetanus as a complication of internal diseases, the simultaneous appearance of tetanus and of other diseases, and the occurrence of tetanus as a sequel of internal diseases are not satisfactorily explained as yet, when injuries are absent. But they all seem to indicate that the tetanus bacillus may find its way into the system in some unknown manner. Some cases of tetanus after concussion or a heavy blow on the neck followed within a few hours by rigidity in the extremities as well as symptoms of meningeal irritation and of tetanus must be included here. But we must be careful not to confound a meningitis which may arise in such occasions with tetanus.

Complications and Sequelæ.

There are cases, and they occur not very seldom, in which after a heavy cold, nasal catarrh, diarrhœa, inflammatory rheumatism, or endocarditis tetanus gradually appears in a mild form. Sore throat and diphtheria are rarely complicated with tetanus, but when they are the bacillus has probably entered through the trachea. We must be careful not to be mistaken in regard to the first signs of these diseases and to take them for symptoms of tetanus. The same caution must be used in regard to parotitis.

Pneumonia, pleurisy, and even slight nephritis may sometimes be complicated with tetanus. Some characteristic cases of idiopathic tetanus are mentioned by Rose, Verneuil, Werner, and others. They occurred especially in washerwomen, servants, masons, and men working in sewers. About twenty-four hours after a chilling of the surface pains in the back and trismus appear, often with a bending of the body in some direction. The rigidity gradually increases, spasms of reflex character occur, and often death ensues. In some cases there is a history of a nail having been stepped upon, but without penetrating the skin; or there are recent or old scars, but sometimes there is no such cause, not even a cold.

Sequelæ.—In cases of gradual recovery, various results of the long illness and of the rigidity are observed, such as hypostatic congestion of the lungs, œdema of the lower extremities, great weakness, and anæmia. Of special importance we may consider the so-called stage of ankylosis, in which we see a rigidity of the members and of the muscles of mastication for a long time after trismus has passed (Rose's sixth stage). Chewing is difficult; the joints are stiff, probably as a result of the chronic rigidity, and the muscles are stiff although their functional activity is preserved, but in impaired degree. They are probably injured through rupture of their fibres, hemorrhages, and degeneration. As further results of tetanus we must mention wounds by biting of the tongue, injuries produced by falls, and finally ruptures of the muscles during severe spasmodic contraction.

Diagnosis.

In the previous sections we have referred to certain elements which serve to establish the diagnosis of tetanus. First of all the clothing of the patient must be entirely removed and a careful search made for any possible wound, especially in the hands or feet, about the nails. Splinters, fissures, wounds, abscesses, and scars ought to be looked for. The genitals, scrotum, mouth, and nose also call for a careful examination. We must inquire whether the patient had been brought in special contact with earth, dust, horses, manure, or sewers, or whether he knew of any cases of tetanus in men or horses.

Then we ought to carefully examine the existing trismus. The index finger should be passed into the mouth of the patient, between the cheeks and the molar teeth, and determine the position of the ascending ramus of the jaw, examining externally and while the jaws are closed and opened as far as possible. If trismus is pronounced we always find a sharp border between the jaw and zygomatic arch, which remains after the mouth is opened, and which is also present even in slight cases of trismus; in healthy people the edge of the masseter cannot be felt when the mouth is open, and even during biting it is stretched only for an instant. We must also see whether this condition exists on both sides, as the muscles are always equally affected in tetanus, and whether there is any abscess, inflammation, or sensitive point in the mouth which might affect the action of the masseters.

Then the degree of trismus has to be tested by opening the mouth and measuring the size of the aperture. The mouth can be closed under such conditions, but to open it beyond a certain degree is absolutely impossible. Even if the masseters are forcibly stretched, they return immediately to the condition of involuntary contraction. The effort to open the mouth produces pain in the tetanized muscles. Then the patient should try to approximate his chin to the chest, which he will be unable to do even in the early stages of tetanus on account of the beginning of opisthotonos. At the same time examination should be made for other causes of this condition; a firm grasp of the neck is painless in tetanus while in meningitis it is very painful; in meningitis we find also enlarged lymphatic glands. Changes in the facial expression, such as the pouting prominence of the lips, the risus sardonicus, and the elevation of the eyebrows, are often absent.

When all the above symptoms are present, we may make a positive diagnosis of the tetanus, but we must be careful not to confound *local* *changes*, abscess, inflammation at the roots of the molar teeth, violent sore throat, or parotitis, all of which are accompanied by fever, with the apyretic onset of tetanus. Difficulty arises sometimes in the differentiation from chronic inflammation of the sphenomaxillary fossa, which leads to spasmodic contraction of the jaw; as also from inflammation of a wisdom tooth, in which there may be no visible external swelling and no pain, but in which the maxilla may be closed for a long time. In such cases a diagnosis is rendered possible by the ability of patients to increase the beginning opisthotonos voluntarily.

Myositis of the muscles of mastication may lead to trismus, but this is usually chronic and is characterized by a tumor-like, sometimes ossifying swelling of the muscles in the temporal region as well as in the zygomatic fossa. Opisthotonos and the other symptoms of tetanus are absent.

Cerebrospinal meningitis, occasionally even *tuberculous meningitis*, may be confounded with tetanus. Ordinarily the fever, which is always present in meningitis, should aid us to a correct diagnosis; then also vomiting, hyperæsthesia, sensitiveness of the region of the neck, and dulness of the sensorium are symptoms of meningitis which are all absent in tetanus. Some cases of traumatic meningitis may easily lead to mistakes, especially if fever is absent, while there are trismus and opisthotonos. The slowness of the pulse and the rigidity of the muscles of the back must then be taken into consideration. But in some cases the autopsy alone can decide the diagnosis. Abscess of the cerebellum is also sometimes confounded with tetanus, especially on superficial examination, and when there is no fever and when opisthotonos is present. Ordinarily tetanus should be excluded in such cases by the constant headache and absence of trismus. We also should exclude tetanus in uræmic opisthotonos without trismus.

Tetany, which is observed especially in pregnant and nursing women, but also after operations for goitre, and in dilatation of the stomach, is characterized by a periodical spasm with rigidity which occasionally lasts a quarter of an hour, and sometimes also by violent fever; rigidity begins in the hands. The spasms may repeat themselves frequently, but are seldom dangerous, though patients often become cyanotic. All these symptoms are absent in tetanus.

Eclampsia potatorum is also occasionally mistaken for tetanus, although there is neither trismus nor opisthotonos to be observed, but solely an occasional local rigidity, starting from some injury.

Permanent tetanus of the extremities is the name given to a rigidity of the new-born which is usually caused at the time of birth by certain deformities of the skull and which involves an arrest of the development of the various faculties; all the extremities or some one only may be affected. The disease remains stationary or may recede somewhat.

Some intoxications, especially by *strychnine*, may often be confounded with tetanus, but the diagnosis is not difficult. This strychnine poisoning is essentially and from the start a reflex spasm; first the lower extremities become stiff soon after the poisoning, then the arms and soon the whole body; the stiffness may cease after a few minutes, but returns on the slightest external irritation. The spasms, at the start very violent and frequent because every motion excites them again, become gradually rarer with the increasing exhaustion and loss of consciousness by the patient, and death occurs after the excitability of the nerves is dulled—but the nerve centres remain irritable to the end. The essential difference between strychnine poisoning and tetanus is therefore the short duration and speedy arrest of the rigidity and the clonic spasms in the intoxication. The rigidity affects soon the whole body and ends usually after a few hours in death, while tetanus begins with trismus, which is constant, and with hands free of any contraction.

In forensic cases every doubt will be removed by the detection of the easily traceable poison.

Although some, probably inexperienced, authors have confounded tetanus with *rabies*, such a mistake appears almost incomprehensible. In rabies all the characteristic symptoms of tetanus are missing; difficulty in swallowing is only occasionally observed in tetanus, while in rabies glottic spasm, and avoidance of the light and air are essential and constant symptoms.

If there is no trismus or opisthotonos, but only reflex spasms in the throat, which disappear after a few days and give way to exhaustion which always ends in death, sometimes with symptoms of paresis, the disease is rabies. It will be hardly necessary to inquire into the etiology, which in such cases is the bite of a dog weeks or months before, to exclude tetanus absolutely. Even after death the diagnosis is easy, because a subdural injection of brain or cord matter into a rabbit or a dog will invariably produce rabies, while the central nervous system in tetanus is not infectious.

Prognosis.

Tetanus ends usually in death, especially after grave injuries with gangrene; in traumatic tetanus the mortality is about 88 per cent., in the rheumatic form 80 per cent., and in facial tetanus about 70 per cent. There are, however, mild and grave cases, according to the time which has elapsed after the injury was inflicted until the attack begins. The later tetanus appears the more favorable is the prognosis. In one-third of all cases tetanus breaks out one week after the injury and then generally becomes fatal; in rare cases this form becomes chronic, but usually its course is very rapid. In two-thirds of the cases the disease appears in the second week after the injury. About 95 per cent. of patients with an incubation of from one to ten days die; of from ten to twenty days about 77 per cent.; of longer incubations about 50 per cent. The later tetanus appears, the slower and the more incomplete is its course. Of 50 early cases there were 10 only of slow course; and 3 only ended in recovery. Of 20 late cases there were 16 of chronic course and 10 only ended fatally. The course of tetanus varies greatly and may last from a few days to several months. About 80 per cent. die in the first weeks, and 50 per cent. in the first four days. Tetanus neonatorum ends fatally within the first week in 70 per cent.

Recovery takes place in very acute cases in about 18 per cent., chronic cases about 30 per cent.; most patients die in the second week after the accident. The prognosis is favorable in incomplete tetanus. In cases of trismus without muscular spasms the mortality is 50 per cent. Even in cases with few and slight spasms we see 30 per cent. of recoveries, and more if the spasms are purely reflex in character. The prognosis is more favorable in cases in which the wound has received early and proper treatment and when early employment of the tetanus antitoxin has been resorted to. Under this treatment the mortality has been reduced to 45 per cent. Intracerebral injections have not hitherto bettered the prognosis so far as my personal experience goes.

Prophylaxis.

As the cause of tetanus has been discovered, we must now try to derive practical advantages in respect to prophylaxis and treatment of the disease from this fact. The discovery of the conditions of the life of the bacillus, the production of tetanus toxins in the wound, and the mode of extension of the disease indicate first of all the necessity of thorough antiseptic treatment of the wound.

The discovery that infected earth and manure, when contaminating the wound, are very active causes of tetanus has shown the necessity of paying especial attention to the disinfection of such wounds and to the removal of foreign bodies from them.

The greater the force inflicting the wound, the deeper small infected bodies may enter and the easier they may be overlooked even in most careful cleansing of the wound. If, then, gangrene or suppuration occurs, the danger of tetanus will be greatly increased. In such cases we must not neglect to cleanse the wound of all foreign bodies and to disinfect it most carefully and thoroughly. The wound ought to be laid open as far as possible, and if its appearance is bad or there is a disagreeble odor more thorough treatment should be begun. I, for example, have succeeded, in a case of infection of the tail of a cat by tetanus bacilli, in preventing tetanus by amputation of the tail twelve hours after infection.

Of course we must not inconsiderately resort to such radical measures, because there is only a small proportion of injured persons, sometimes more, sometimes fewer, exposed to tetanus infection. In a case in which many persons are injured at the same time and place and by the same means, as, for example, in a battle or on the occasion of some catastrophe in civil life, and one of these shows signs of commencing tetanus, then we must of course treat the wounds as radically as possible. They should be enlarged and disinfected with a three-per-cent. carbolic acid or cresol solution in order to protect the patients thereby from infection or to make the disease lighter if it has already begun. Wounds on the feet require especial attention; then those of the hands; wounds of the head or neck are less dangerous, as they rarely are followed by tetanus. We also have to take especial care to protect the wound from subsequent infection. When we are obliged to cut deeply we must be careful not to introduce tetanus spores into the wound by our instruments, as these spores are very resistant to the action of antiseptic solutions. We also have to instruct people as much as possible not to cover wounds, especially those produced by insect bites, with mud or cobweb (a common domestic practice), as these may contain tetanus spores. In hospitals, especially in the surgical wards, the bedclothes and the underclothing should be changed frequently. The hands and mouth of the patients must be disinfected daily, and dust must be kept out of the wards as far as possible; the furniture, floor, and walls should be cleaned with antiseptics. Overcrowding of the wards is very dangerous, as is also the practice sometimes resorted to in military hospitals of allowing the patients to lie on the floor. I have seen a case of tetanus occurring in a patient whose bed was made on the floor. The floor itself must be kept as clean as possible. The shoes of the visitors should be cleaned outside with antiseptics.

In barracks and in stables, especially those of the cavalry, we have to be even more careful with injuries. If one of the horses has had tetanus, the stable must be disinfected thoroughly and the manure removed; all currycombs and the like, the straw, and the hay should be burned, and the earth should be dug up and replaced by fresh and disinfected earth. In case of a horse being affected with tetanus, the soldiers and attendants should be thoroughly examined, and any present or future wounds should be thoroughly disinfected. These measures will not only render tetanus rarer in war, after operations, and in those especially exposed, but they will also be useful in the case of apparently trivial injuries in preventing the disease in persons who, if not treated, would quite probably be attacked by it. Rose's statistics have proven that not only has tetanus following operations and burns been markedly lessened of late, but that in Germany it has become much rarer as a result of more general diffusion of knowledge concerning it among the masses and increasing cleanliness. In Roumania, however, it is still very frequent, especially among those who are careless in their person. It is also very evident that the course of the disease, once it has been acquired, is more favorable under improved hygienic measures.

Roux and Nocard recommend preventive inoculations in the case of injury in which tetanus infection may be suspected. In experiments on animals injection of antitetanic serum has prevented the outbreak before and even after infection.

We shall discuss the preparation of the serum below, and here we will only say a few words about its proper application.

In analogy with the prophylactic inoculations employed in rabies and diphtheria, Roux and Nocard, Tizzoni, and Behring, have successfully attempted to prevent tetanus by serum injections. In veterinary surgery especially they found that horses thus treated before castration or hoof operations were never attacked by tetanus. The cost of the remedy and the rarity of tetanus after injuries will, however, not allow of any frequent use of this serum, and a decision as to its prophylactic value is therefore rather difficult. But it is highly advisable to try it in cases in which several persons have been injured by the same cause and one of them has been attacked by tetanus; as also when a case of tetanus has occurred in a hospital or when an operation which is sometimes followed by tetanus must be performed without the possibility of absolute asepsis. Prophylactic serum is now manufactured of the strength of 20 units in 2 c.c. It is said to give protection against infection for four weeks, and this is usually sufficient. If an injection is made immediately after the injury or before an operation, 1 c.c. is a sufficient dose; but if made at a later period or in case of grave injuries, 4 c.c. must be injected. In horses double this amount is required. In the absence of antitetanic serum, I would recommend in these cases an injection near the wound of from 2 to 5 gm. of a solution of one-half-per-cent. cresol or of one-per-cent. carbolic acid in physiological salt solution or in artificial serum.

Experiments with dogs have shown that daily injections of a carbolic-acid solution may prevent tetanus in case of a moderate infection. The same result has been obtained in rats and in rabbits, especially if begun a few days before infection and continued for a week.

Treatment.

It is difficult, even for one with a large personal experience, to form an opinion as to the efficiency of the various remedies used for tetanus, when we remember how cases of this disease vary. Thus, I am able to record 6 cures out of 10 consecutive cases of tetanus; the statistics also of Friedrich, Körtes, Marvan show about 50 per cent. of cures, while Rose records 65 per cent. of cures in his first series of statistics, and 17 per cent. in a later one. At one time, on the other hand, there were only about 6 per cent. of cures to be noted. On the whole, about 12 per cent. of recoveries may be assumed, as we learn from the very exhaustive statistics of Rose.

Obviously statistics, embracing only about twenty cases, will give us very little information as to the success of any one method of treatment. As a general thing, tetanus responds to various curative agents, and the statistics of cases expectantly treated shows us worse results than when any active treatment is employed.

It stands to reason, however, that we must not ascribe the cure of any single case to the method of treatment employed; and we can speak of an agent as actually curative only when (1) a large percentage of recoveries is obtained in a great number of cases which have been all treated by the same method; (2) recovery follows, apparently as a result of treatment, in cases which have made their appearance one week after the injury, and already present well-marked trismus on the first day; (3) if a marked improvement, not usual when the disease runs its natural course, takes place immediately following the institution of treatment; (4) the critical, sudden disappearance or positive arrest of the symptoms after the beginning of treatment. This latter would afford us a positive and convincing proof of the curative action of any remedy; but up to the present time no such result has been attained under any treatment.

In the absence of this criterion the abortive course of cases which had a serious beginning will also afford a presumption of the curative value of a remedy, although in rare cases such a course may also occur without any special treatment.

As more than eighty per cent. of cases of tetanus are caused by wounds the infection of which leads to tetanus, we are imperatively obliged to disinfect the wound thoroughly, or where this is impossible to amputate the wounded member.

Although in rabies, for example, this method does not yield good results, since the virus has already inundated the central nervous system once the disease has actually begun, it is demanded in tetanus, in which affection the virus is present only in the wound, whence the continuously excreted toxins are taken up into the system. It is only in cases in which many and extensive wounds are present that this indication must sometimes be neglected. It is certainly true that the toxin has already injured the nerve cells before the occurrence of symptoms, and that the cell lesion cannot be influenced by treatment of the wound at the beginning or at least when the disease is fully developed; but we have already seen that tetanus spreads gradually and progressively, which fact obviously bears on the gradual involvement of more and more cell tracts. This extension may, at least in the first stages of the disease, be arrested by destroying the foci of infection. I have myself demonstrated (*Annales de l'Institut de Bactériologie,* Bucharest, 1892) that tetanus can be prevented, not only as Kitasato claims, one hour after inoculation in the tail by amputating the latter, but that in the cat when inoculated in the tail, the fully developed attack may be changed into an abortive one by the amputation of the tail. I have obtained the same result, as a rule, in experimental amputation of an infected extremity in the guinea-pig. Thus experimental pathology also gives us a positive indication for the value of the removal of the diseased part, especially during the first stages of the disease.

Local Treatment.

We will therefore always do well to cleanse the wound carefully and to lay it open freely in different directions, in order to arrest the growth of the anaerobic bacilli, and to prevent their manufacture of toxins. I cannot too strongly insist upon the necessity of the destruction of the toxins by means of carbolic acid, which has given extraordinary results in the dog. I am less partial to the use of escharotics, as these irritate the tissues on the one hand, on the other they favor the formation of a crust, which protects the tetanus germs in their anaerobic growth. Of much greater value is total excision of the wound, exposing the deeper tissues, which should be thoroughly soaked with carbolic acid or creosote. In many cases amputation of the member cannot be avoided. The amputation of a member is in itself a grave operation. but it is indicated in extensive gangrenous wounds and injuries, as these are also inimical to life even when tetanus is not present. As, however, in these usually most severe cases of tetanus the organism is greatly debilitated, the operation may easily induce a state of exhaustion while seeming improvement takes place, and even slight shock may cause death. At all events, it is better to forego the operation in cases of great exhaustion as well as in the stage of reflex spasms. It is especially indicated in the beginning, when the rapid commencement and the violence of the symptoms would lead us to fear the worst. Unfortunately, however, the patient, who looks upon the disease with too much unconcern at this time, at first usually refuses the operation. Thus, the results of amputations undertaken for the treatment of tetanus are not very encouraging. Death very frequently occurs on the day of operation in consequence of exhaustion, as has been previously said. A few cases in which the amputation was done quite early in the stage of opisthotonos, especially when only a finger or toe was amputated, have ended in recovery, but it could not be satisfactorily demonstrated that the favorable issue was attributable to the amputation; as in some cases the tetanus has increased after the amputation, the favorable termination in other cases cannot very well be attributed to the operation. We may therefore say that amputation, when it can be performed early, the patient being otherwise in robust health, is to be recommended, especially when only a small portion of a member is involved; but it can hardly be said to be effective in the later stages, and in cases of extensive and grave injuries. It is true there are about forty cases on record of cure after amputation, but they are by no means convincing, as we are not informed what ratio these recoveries bear to the total number of amputations; moreover, the history in a number of these cases was not carefully and fully recorded, and the cure in many cases could be more justly attributed to other factors. Thus Rose reports eleven cases of amputation with one recovery, and in this case the tetanus increased in severity for several days after the operation. On the ground of this experience I am unable to agree with Rose, who claims that of all methods of treatment of tetanus amputation has the greatest claim. To me it seems that by a careful opening of the wound and the removal of all suspicious material, we are able to do much more.

In gangrenous and ulcerating tetanus deep and long incisions should be made; in tetanus after pistol wounds, the canal should be widely opened; not only should splinters be removed, but at the same time the wound should be widely opened and the granulations scraped away. The surface of the wound should then be carefully irrigated with carbolic-acid solution and should be treated open.

In this matter too much stress cannot be laid on the fact that the patient suffering from tetanus should not only be thoroughly examined, but that any operation necessary should at once be carried out. Here in Bucharest the wound has been treated differently in most fatal cases, and I have often found at the autopsy infected splinters deep down in the wound. An operation would obviously have saved many of these patients.

What may we expect from the nerve section sometimes practised in tetanus? After my demonstration that the poison of rabies passes from the wound along the nerves to the central nervous system, we might be led to assume a similar action of the tetanus poison and might hope, therefore, by dividing the often greatly swollen and inflamed nerves of the injured locality, to hinder the extension of the poison. The nerves are, however, not the only, not even the principal, route by which the poison extends. It has been frequently demonstrated that the poison of tetanus is especially found in the blood, and thus bathes the whole organism and reaches the localities from which it exerts its effects. In the nerve itself, however, the toxin has not been found up to the present time. But section of the nerve has been advocated on other grounds, for it has been demonstrated that the spasms of tetanus do not occur in a part the nervous supply of which has been cut off, and that if trismus is already present it will relax.

Curiously the section of the sensitive nerves or of the posterior roots produces a similar although imperfect action, on which Courmont and Doyon based their hypothesis that tetanus was produced by the excessive irritation of the sensitive nerves of the injured region, a view which is rather disproved than corroborated by the incomplete effect of section of the sensitive nerves. The fact, also, that the section of the sensitive nerves previous to the outbreak of tetanus by no means retards the outbreak, speaks against this view, the corroboration of which indeed would have been an indication for the nerve operation. The muscular contraction in tetanus is originated in the nerve centres, but normal irritation and conduction of the sensitive nerves in this disease induce an excessive reflex action, just as happens, according to Hering's experiment, in poisoning with strychnine. This observer, after section of the spinal cord, made a direct application of strychnine, especially to the anterior horns. No convulsions followed this application, but if now the sensitive nerves were irritated increased reflex movements were always excited. The cells of the anterior horn were therefore rendered highly irritable by the strychnine, and the same effect might experimentally be shown to be produced by the toxin of tetanus. Nevertheless, we shall do well to attribute to the sensitive-nerve conductions some influence on the symptomatology of tetanus, as the weakening of the spasm after section of the nerve cannot be denied. As a fact, surgeons did long ago practise section of nerves with a seemingly favorable result in tetanus. In some cases a cure was obtained by simple neurotomy (Wiedemann, 1792) or neurectomy, and also by stretching the nerves (P. Vogt, 1876). In none of these cases, however, could the result be attributed with any amount of certainty to the operation. It is worthy of note that nerve-stretching and other operations on the nerves which have been advocated in the treatment of various diseases have frequently produced tetanus; a fact which we may explain on the assumption that the operations might have been the means, in the presence of tetanus bacilli, of awakening the latent excitability of large nerve cells.

Rose rightly points out the difficulty of finding the right nerve, when we are dealing with extensive or multiple injuries. This author admits the existence of only two cases demonstrating the success of neurectomy, but these do not strike me as convincing, since in one case (Murray, 1832) tetanus is said to have appeared ten hours after the injury, which does not seem probable, and the second case (Pecchioli, 1893) was also treated with other remedies. It is a pity we do not know in what number of cases the operation has been unsuccessful, as such cases are as a rule not reported. Doubtless the operation has been frequently performed, and the meagre reports would therefore seem to point to only very moderate success. Nevertheless, I would not counsel against section of the nerve in cases of tetanus of extraordinary rapidity and violence, if the nerve to be cut could be easily determined.

INTERNAL TREATMENT.

It might be assumed *a priori* that in tetanus, as the essential symptoms consist in a hyperexcitability and consequent excessive contraction of the muscles, calmative remedies would be indicated, especially as the symptoms of tetanus are quiescent during sleep. The patients, however, hardly ever sleep, probably because the offshoots of the excited cells are continually stretched and in contact with other neurons, so that the waking state is maintained. Sleep, therefore, without a doubt depends upon the same relaxation of the hyperexcited motor cells as brings about the cessation of tetanic spasms. If we had any remedy by means of which we could effect this relaxation, or even benumb the areas of excessive irritability, we should be justified in regarding it as a specific in tetanus. But even the most powerful hypnotics frequently fail us in tetanus, as the irritability of the cells resulting from the action of the toxin of the disease is dependent on internal changes, so that it cannot be overcome either wholly or partially by the remedies employed. Nevertheless, hypnotics are to be looked upon as valuable adjuncts in the treatment of tetanus, as they obviously support the endeavor of the organism to lower the increased excitability of the cells. It goes without saying that we must not underestimate the deleterious effects of these remedies.

According to Dazille *opium* is the one and only remedy in tetanus. It had already been warmly recommended in the last century by J. Louis Petit. Stütz employed carbonate of potassium alternately with opium in tetanus, and was able to obtain a considerable number of cures in light cases. It is not essential to discuss the incorrect theory upon which this author bases his treatment, but we may safely employ this combined method in the absence of any positively curative remedy. We would especially advise the retention of opium, although there are some theoretical objections to it and a few authors warn against its use. The initial irritability, even convulsions, occurring in opium poisoning need not be taken into account in view of the peculiar nature of tetanus, but the hypnotic action of the drug must be kept in view. It is best to order in the beginning stimulating doses of hydrochlorate of morphine, as the amount of morphine contained in other opium preparations is variable; and we must not be afraid of giving large doses, for incredibly large doses of opium, far exceeding the maximum daily dose of 0.5 gm. (gr. viiss.), frequently produce neither sleep nor even improvement in the symptoms. Nevertheless, in some cases recovery ensues, although in the beginning the administration of opium fails to induce sleep or to influence the symptoms favorably; the influence of the drug in such cases seems to be somewhat problematical. In other cases in which opium has been given together with various other remedies, it is difficult to determine to which the cure ought to be ascribed. Nevertheless, we are justified, in cases in which recovery has taken place under the opium treatment alone, to attribute to the latter some influence, as many of the recorded cases were of a very grave character and of the kind which, if not subjected to treatment, nearly invariably end in death. We must of course not underrate the influence of hospital care, of artificial feeding, and of the avoidance of harmful external influences, and must admit that such measures, even in the absence of internal medication, are of some value in tetanus. Finally, however, if we take in consideration the fact that most patients suffering with tetanus now receive some preparation of opium, and that the mortality of tetanus still exceeds eighty per cent., we shall not be led to expect too much from this treatment. This should not deter us from employing opium, but the drug should be combined with other remedies whose utility has been more or less proven. At all events, I do not agree with Rose, who used opium or other remedies by themselves alone, so as to be able to draw comparisons between them. We should rather always keep in mind that man is not an animal to be experimented upon, and that we should make use of all kinds of remedies to cure our patient. Of course, we should not administer together remedies which are antagonistic, but apart from this we should make use of everything that has been found useful empirically, regardless of the physiological action of the individual drugs. We should make an effort to have our patient take opium internally, in the form of the tincture perhaps, but, better still, of a solution of hydrochlorate of morphine in the maximum doses. We find in the literature reports of the cure of several cases in which very large doses of opium had been given (5–10 gm. = gr. lxxv.–cl. a day). Furthermore, opium and morphine have been administered in the form of clysmata, especially, however, by hypodermic injections.

Chloral hydrate has also been used successfully, but only in maximum doses, at least 6–9 gm. a day (gr. xc.–cxxxv.), each dose representing 3 gm. (gr. xlv.). It also seems to act well by enema, and may sometimes be advisably so given since, because of its disagreeable taste, it may when given by the mouth excite reflex spasm, especially of the œsophagus. Enemata applied with a soft rectal tube are to be recommended only when the tetanus has not yet travelled down too far. Cases of recovery are known in which increasing doses (12–24 gm. = ʒ iii.–vi.) have been employed.

Recently chloral has been combined with morphine, the two being given alternately and in maximum doses. It is difficult to form an opinion as to the action of chloral hydrate from the observations made up to the present, as various other remedies have as a rule been employed at the same time. It is true, there are a few very grave cases on record as cured in which large doses of chloral hydrate were given, and the patient was kept in a somnolent condition throughout. These are, however, balanced by numerous deaths under this treatment, a small number of which could justly be ascribed to œdema of the lungs produced by the chloral. On the whole, the statistics of the chloral, or chloral-morphine, treatment of tetanus do not seem to be more favorable than those when other non-specific hypnotics and antispasmodics, such as cannabis indica, paraldehyde, and bromide of potassium, which have been employed sometimes in tetanus in conjunction with other remedies without any definite result. In one case of slowly appearing and slowly developing tetanus, which came under treatment with well-developed trismus, I was able to procure some sleep with trional. This patient recovered under the use of carbolic-acid injections. The indication therefore is to make use of the recent hypnotics, especially sulphonal and trional, in doses of perhaps 1.5–2 gm. (gr. xxii.–xxx.) or more at night. It is of course necessary not to neglect the specific treatment of the disease in conjunction with these remedies.

Curarine.—As this drug paralyzes the motor-nerve endings, it was thought it might be useful in tetanus. As a fact, we are able promptly to check strychnine poisoning by means of curare; in tetanus, however, especially in the violent acute cases, this remedy has usually failed to afford relief.

When giving the drug to man, we must advance very carefully, give very small doses, repeating them frequently. Its action, especially in subcutaneous injection, may be very powerful, and only a few milligrams (say gr. $\frac{1}{60}$–$\frac{1}{30}$) should be used as a single dose, while, when given by the mouth, the dose may be much larger. Man has greater resisting power to curare than the dog, a lethal dose for the latter being 0.01 gm. when injected subcutaneously, while the fatal dose for man is 1–1.5 gm. (gr. xv.–xxii.) of the crude drug when taken by the stomach. There are no cases on record of tetanus cured under the curare treatment, but, on the contrary, it seems to hasten death. The same may be said of *Calabar bean*, which has been injected subcutaneously in the form of salicylate of physostigmine in daily doses of 0.01–0.03 gm. (gr. $\frac{1}{6}$–$\frac{1}{2}$). Although a few mild cases have ended in recovery under this treatment, the use of the drug has been abandoned, as it was found that it did not act so well in grave cases as morphine injections.

While drugs exhibited internally are inefficient, as a rule, being frequently not absorbed, we are able to employ external remedies with greater success. Moist heat especially, which brings the blood to the surface and causes relaxation of the muscular tissue, has an evident quieting effect on the spasm. To this is also added the fact that the tetanus bacillus thrives best within certain limits of temperature. If it were possible to regulate the temperature deep down in the wound for a certain period so as to destroy the bacillus, this would obviously come to be the proper treatment. We have demonstrated that the frog and the chicken are immune to tetanus; when, however, the frog is warmed, tetanus may make its appearance. On the other hand, it is possible to increase notably the secretion of the wound and especially that of the skin by moist heat, and thus to favor the excretion of the toxins. Finally, the patient is placed in a restful state by carefully enveloping him in moist hot sheets, which, especially in the stage of reflex spasms, affords great relief. When we ask ourselves, What has moist heat so far accomplished in tetanus? the accessible material does not, it is true, give us much information. It certainly, however, has not done any obvious harm. It goes without saying that when giving a hot bath, even a permanent one, the placing of the patient in the bath, and the momentary irritation to the skin by the hot water will do harm to the patient, just as would any other irritant, and might excite dangerous spasms; for this reason it is probably better to avoid the bath and substitute for it the warm moist pack, systematically and continuously applied. Its action is manifested in the quieting of the patient, in the less frequent occurrence of the paroxysms, and also in a copious perspiration. Especially in the rheumatic form of tetanus this method seems to have done good, as the moist heat also acts favorably on the rheumatic element in these cases. Obviously we cannot expect everything from the moist heat, it should be conjoined with the administration of opiates, especially also with local and specific treatment.

Rose believes also in the application of cold, and especially the gradual withdrawal of heat, and he ascribes to this some of his successes; the observations bearing on this point are, however, too few and incomplete to be made use of here. In any event cold baths must be strictly avoided in tetanus, as they might cause shock and even sudden death.

Carbolic Acid.—Injections of carbolic acid were first recommended by Baccelli on the strength of a cure obtained in a very grave case of tetanus.

I have employed this method—which, it is true, does not correspond to any theoretical indications—in a number of cases with success. In the first instance, carbolic acid acts as an anæsthetic, then as an antiseptic, and as an antidote to the toxin of tetanus, as has been demonstrated by Kitasato. I have experimented with this remedy, in the first instance, on dogs, by injecting five times a day 10 gm. (ʒ iiss.) of a one-half-per-cent. solution of carbolic acid on the appearance of the first symptoms following inoculation with the tetanus poison. While the control animals succumbed to tetanus, all the dogs treated as above were saved, the symptoms nearly entirely disappearing on the ninth day after infection. In these cases I was able to demonstrate that the muscular spasm frequently began to relax at the point of injection. When the symptoms decreased the injections were also made less frequently. This method was employed in experiments on other animals successfully. Of six infected pigeons three were injected eight times a day with 1–2 gm. (♏xv.–xxx.) of a one-per-cent. solution of carbolic acid, as soon as the symptoms of infection appeared; all of these recovered, while the three control animals died of tetanus. The same treatment carried out in rabbits, also, saved the infected animals, while rats were only in rare instances cured by this treatment. Nevertheless, the general result of this treatment is very remarkable and hardly less manifest than the action of antitetanic serum. The animals cured were not, however, absolutely immune to new tetanus inoculations, but succumbed after repeated injections of toxins.

This remarkable result led me to apply Baccelli's method to man. It has been found in the case of animals that the disease occurring in those not easily infected (dogs, pigeons), and particularly the lighter forms of infection, were cured by the carbolic injections, and it was therefore to be presumed that in the human subject also the lighter forms, at least, of the infection could be influenced by this treatment. In cases in which it was tried I was able to observe a diminution of the symptoms in the neighborhood of the points of injection. I employed in man a one-half-per-cent. solution of carbolic acid, which was injected along the spinal column, beginning at the neck, in doses of 5–10 gm. (ʒ i.–iiss.) every two hours. Of four patients treated in this manner three recovered, while the fourth, who had the disease in very aggravated form, died from suffocation on the day of treatment.

This case was that of a young man who was suffering from an extensive gangrenous contused wound of the thigh, and who began to have symptoms of tetanus on the fourth day. Trismus was marked from the beginning, and was succeeded on the second day by opisthotonos with violent muscular spasms. On the third day the injections were begun, but the patient died on the same day in a suffocative attack preceded by rise of temperature and increased pulse rate.

The first case in which the carbolic treatment was used was one of contusion of the finger followed on the twelfth day by tetanus. This developed on the third day into extreme trismus and opisthotonos. The carbolic-acid injections were carried on for eight days, the opisthotonos beginning to relax, even after the first injection, in the parts about the point of insertion of the syringe. The muscular spasms recurred from time to time even up to the termination of treatment, but in decreasing intensity. The trismus also, which was fully developed on the third day of treatment, only gradually improved, and was still present at the end of a fortnight. There was also difficulty in eating and talking. This patient received during each of the first few days of treatment eight injections of a one-half-per-cent. solution of carbolic acid, the daily number of injections being reduced later to six and four. During the latter days of treatment a moderately intense carbolic-acid urine made its appearance, and the treatment was discontinued after a remarkable improvement. Eighteen days after leaving the hospital, this same individual had a slight return of trismus and stiffness in the back, but this disappeared almost entirely after renewed treatment with carbolic injections for four days.

Another case relates to a florist's helper who received a severe contused wound in the right hand which was covered with dirt. Ten days later nearly total trismus supervened. This case occurred in the same section of the hospital as the first one, but three weeks later. On the first day of the disease there was total trismus, on the second day opisthotonos and insomnia appeared. The wound was freely opened and cleansed, and the carbolic-acid injections were begun. On the third day opisthotonos was not so marked; three strong spasms occurred. On the fourth day there was a slight improvement already noticeable, especially in the opisthotonos, and the trismus was not quite so marked. There were three violent spasms accompanied by cyanosis, and a sensation of choking. During the night the patient slept some and the trismus was somewhat improved, and on the fifth day he was able to open the mouth a little (1 cm.). The spasms recurred quite frequently though they were less severe. From now on improvement rapidly took place, and by the end of two weeks the patient was well.

In the third case there was a compound fracture of the humerus, from a fall off a scaffolding, and dirt and brick dust were deeply embedded in the wound. At the end of twelve days, when healing was progressing favorably under thorough cleansing and conservative treatment, trismus suddenly made its appearance in the morning. The mouth could be opened about 3 cm., and there was slight opisthotonos. Carbolic-acid injections were at once administered. On the first day trismus was nearly complete (1 cm.). No sleep could be obtained at night, and on the following day the process remained stationary. On the third day there was slight opisthotonos, but the jaws could be opened a little wider. There was one moderately severe spasm. From this time on recovery was rapid. This was a case in which the disease was ushered in by violent symptoms, but which was aborted as a result of treatment.

Although Baccelli's treatment, which according to Italian observers at first furnished good results, is becoming obsolete, probably on account of the introduction of the modern specific treatment, I am, nevertheless, constrained to mention it, as it has given me such good results. We will see also that the statistics of the antitoxin treatment do not show any better results. We cannot deny, it is true, that, given the rapidly changing picture of tetanus, these three patients might have recovered spontaneously; but two of the cases were of a severe type, and, nevertheless, recovery rapidly followed the institution of this treatment, while in the third case the attack seems to have been aborted. In only one case a few symptoms of carbolic-acid poisoning were noted as a result of the great number of injections. In one case œdema occurred about one of the punctures, but it disappeared after a few days. As a result of my experience, I feel justified in urgently advising the injection of a carbolic-acid solution in the manner described in all cases in which the tetanus antitoxin cannot be obtained.

Iodide of Potassium.—Having discovered that iodine rapidly weakens the tetanus toxin, I undertook a series of experiments to determine the action of this remedy in tetanus, and demonstrated its prophylactic and therapeutic value in the case of dogs. In 1893 I undertook a series of such experiments with favorable results. One of these was as follows: A dog was inoculated in the lower part of the back with 3 c.c. of a virulent culture. After ten days general tetanus developed. The following day 5 c.c. of Lugol's solution of iodine was administered, and then 10–30 c.c. of the solution was injected daily for eight days. On the tenth day the animal was well. These iodine injections might perhaps be given alternately with those of carbolic acid in cases in which the antitoxin could not be obtained. The injections produce only a temporary irritation, at least not so much as trichloride of iodine, which I employed in one case in the human subject.

Narcosis has been frequently induced in tetanus, either once or repeatedly or prolonged for a considerable period. In the same manner as sleep, narcosis induces a relaxation of the spasms in tetanus; but as soon as the narcotic effect ceases, the symptoms of tetanus return, frequently with renewed intensity. Whether chloroform or ether or a mixture of both is used, there will always be some irritation of the mucous membranes in the beginning, and this may be so pronounced as to excite a spasm. The spasms so induced may be very violent, and in such a case it will be necessary to push the anæsthetic rapidly to complete narcosis. It is unfortunately true also that death may result from heart disease at the very outset of the administration of the anæsthetic.

When the narcosis, however, has become deep, a surprising picture is presented. All the symptoms have disappeared, the muscles are relaxed, respiration and the heart's action are quieted, and a deep sleep has overtaken the patient; even after the withdrawal of the chloroform and the return of the patient to consciousness this amelioration in the condition may continue for a short time. It might therefore be proper to continue the narcosis until the toxins of tetanus have been eliminated, and, in fact, the narcosis was so continued in some cases for hours, and other cases are on record in which a cure has been obtained by this means. This prolonged narcosis is, however, dangerous and frequently leads later on to anæmia and cardiac paralysis. Especially in tetanus is the administration of ether or chloroform surrounded by manifold dangers. We have already referred to the irritation of the mucous membranes, which may excite a spasm at the outset. During the stage of complete insensibility the patient seems to be out of danger, but after the action of the remedy ceases, the symptoms of tetanus are again developed, and not infrequently a violent spasm comes with returning consciousness and in the course of it the patient succumbs.

It is clear from the foregoing that general anæsthesia can hardly be recommended as a curative measure in tetanus, although it is of course indicated in any operation that may be needed, and especially in the radical treatment of the wound, or in cases in which nutrition is impossible on account of the absolute trismus present.

The nutrition of the patient is of the greatest importance, as many patients with tetanus succumb in consequence of insufficient or altogether unsuitable nourishment. It is true, we may administer food by the rectum, but when tetanus has made its appearance and reflex irritability is present, this will hardly be possible. Under all circumstances enemata are to be given with the greatest care and through a soft rectal tube. Digestion in tetanus appears to be very defective. We should therefore look after the feeding of our patient from the very beginning, and fix a wedge between the teeth in order to keep a small opening through which liquid and semi-solid food, prepared foods, eggs, etc., may be administered. Alcohol, and especially large quantities of wine, has seemed to be useful in some of my cases. Cinchona and chinoidin may also be used with benefit to sustain the patient's strength. In case of threatening starvation, we shall have to resort to chloroform inhalations, so as to be able to administer liquid food through the œsophageal sound while the patient is under the influence of the anæsthetic.

It cannot be sufficiently insisted upon that the patient can be successfully fed and his life preserved only by a very conservative treatment and the avoidance of all sudden or violent measures.

General reducing measures, especially venesection, purging, blistering, salivation, and sweating, have been employed in trismus from time immemorial. But at the present day these measures have lost in great part the repute they formerly enjoyed. We now know that the poison of tetanus acts not so much through a general hyperæmia of the central organs as by a peculiar chemical process on portions of the motor nerve cells, and we accordingly cannot expect any good results from general blood-letting, eliminative measures, or derivation.

Tetanus, as we know, frequently occurs in greatly emaciated and anæmic persons, and is, if possible, more dangerous in these than in robust individuals.

Rose, it is true, mentions the increased weight of the brain in tetanus, and I have also been able to demonstrate it in some cases, while in others again nothing of the sort was found. We are obviously dealing here with a greater turgescence and hyperæmia of the brain, but, as mentioned before, this is not the essential process. Furthermore, it is by no means certain that the fluids gravitating towards the nervous centres may not have a curative effect, for we know that hyperæmia and even inflammation are to be regarded as directly curative processes in certain diseases. In tetanus especially, in the course of which we know that an antitoxic substance is found in the blood and other fluids (bile), rendering them antidotal to the infectious agent or its products, the abstraction of blood with consequent lessening of its antitoxic action is hardly indicated.

Nevertheless, cases are on record of recovery after heroic bleedings, although it may be questioned whether the cure resulted in consequence of, or in spite of, the venesection. At the very beginning of the disease when the brain is bathed in blood rich in toxin, we might possibly expect some good from phlebotomy; but, on the other hand, when the symptoms appear, the central nervous system is already so altered that the abstraction of blood will more likely have no effect upon the course of the disease. It is also questionable to what extent the withdrawal of blood will prevent the continued formation of toxin. Indeed, in this as in the other non-specific measures, there are many obscure points which can be cleared up only by careful experiment.

SPECIFIC TREATMENT.

After tetanus had been recognized as an infectious disease, its bacillus discovered, and its toxin found, pathologists directed their endeavor to the discovery of a specific substance which would prevent or cure the disease. At first it was believed that the bacilli excreted the toxins, but that they contained within themselves antitoxins which might be used for the cure of the disease. We have seen that this is not the case, but that the antitoxin is supplied by the organism.

In the first place, it has been demonstrated that the tetanus antitoxin may be formed in filtered cultures, therefore from soluble products of the bacilli, and the endeavor has been made to obtain these products (toxins) as pure and as concentrated as possible.

Knud Faber and Kitasato have demonstrated that the filtrate of tetanus culture produces tetanus. Especially virulent cultures produce a toxin in bouillon after eight days, $\frac{1}{10}$ gm. of which is sufficient to kill a mouse. If the culture is kept at 37° C. for a long period it loses much of its toxicity, so that now larger doses, probably several milligrams, are necessary to kill a mouse. When exposed to direct sunlight the toxin becomes weakened in a few minutes, and is totally destroyed in one day. Also when exposed to the air, or kept for any length of time in any way, it gradually loses its effect. In the dried form, on the other hand, it retains its strength better. A 0.55-per-cent. solution of hydrochloric acid will destroy the toxin of tetanus in about an hour. So also a 1.5-per-cent. solution of carbolic acid, 0.3-per-cent. solution of caustic soda, or a 1-per-cent.-cresol solution. Other acids and antiseptics are less efficient.

These remedies, however, cannot, as a rule, be employed with success to render the poison innocuous in the system, as they are changed in the organism to inactive matter. Carbolic acid and cresol are the only ones, as we have previously seen, with which we may attack the poison of tetanus in the organism with some hope of success. Naturally the amount of toxin in the organism of the patient is very variable, so that we are obliged to introduce large quantities of carbolic acid into the body in order to be sure to obtain its antidotal effect on the toxin. Heating the toxin to 55° or 60° C. (131° to 140° F.) also destroys it, but such high temperature can of course be applied only to circumscribed parts of the body, with a view to hinder the formation of toxin.

While under favorable circumstances, which we are, however, not always able to control, toxin is formed in the culture in large quantities, there are some cultures which habitually furnish but little toxin, but which may under favorable conditions give rise to the formation of larger quantities. Anaerobiosis, the composition of the food, the temperature to which the cultures are exposed, and especially the time at which the toxin is formed in the cultures, are factors of importance. The dry, pure preparation obtained by Brieger and Cohn is two hundred times the strength of the strong toxin of Kitasato, so that about 0.23 mgm. is sufficient to cause a fatal tetanus in man.

The toxin acts locally, like the tetanus culture, but somewhat more rapidly. According to Kitasato its earliest effect is within four hours, its latest eight days after inoculation, according to the susceptibility of the animal experimented on and according to the amount of toxin injected. At all events, we cannot discern here a stage of incubation, which leads us to conclude that the poison is elaborated in the body, becoming active then. In man the earliest cases of tetanus were observed from two to four days after the entrance of the infectious material into the body, but this period bears hardly any relation to the time which passes between the reception of larger amounts of poison and the outbreak of the disease. At all events, the conditions which exist in natural infection are much more obscure than those in experimental infection.

In man, as we have already seen, the trauma, the association of bacteria, and the general condition are all to be considered, and hardly in any case are we able to assume poisoning by a pure tetanus culture. The period of incubation in man bears no relation to the progressive though slow activity of the bacilli or of their poison, but, as a rule, the tetanus bacilli will not become active for a certain time after the trauma until the local conditions become favorable to them, and the time when their growth begins and that when a sufficient amount of poison has been formed nearly always escape our observation.

The toxin of tetanus has not yet been obtained in absolutely pure form, and it can be recognized only by the results of experiments.

It is known that various chemically pure substances have for a long time been extracted from the tetanus toxin. Thus Brieger has obtained from bouillon cultures of tetanus bacilli (?) a base, "tetanin" ($C_{13}H_{30}N_2O_4$), in the form of a crystallized double salt of platinum, which acted as a poison in small doses to mice, causing a lethargic condition of spasm and tonic convulsions; also a second base, "tetanotoxin," which caused paralysis in experiments on animals; and other substances which have not been carefully described; among the latter is one which causes an exquisite state of tetanus. Perhaps, however, this substance contained true tetanus toxins as an admixture. In one case this observer also found "tetanin" in the amputated arm of a patient suffering from tetanus. After poisonous substances had been discovered in the alcoholic precipitate of anthrax cultures (Hankin), Brieger and C. Fraenkel employed this method also with other cultures, especially with tetanus cultures, and they certainly obtained a soluble preparation from the alcoholic precipitate of tetanus cultures, which killed mice within forty-eight hours, with symptoms of tetanus. This same preparation, but in a weaker state, was obtained in larger or smaller quantity from the organs of animals which had succumbed to tetanus. Evidently these preparations also contained tetanus toxin, but it was not pure, nor was it an albuminoid body, as it has been demonstrated that cultures of tetanus with their toxins do not form on exposed surfaces. Lastly, Cantani has also obtained two bodies from tetanus cultures, as well as from other bacterial cultures, one body which induces fever and diarrhœa, "pyrotoxin," which, however, is no specific. In respect of the modern specific therapy the tetanus toxin which is obtained by filtration and evaporation *in vacuo* alone is of any special interest or significance. To make proper use of this we must first study its action on the organism.

What are the changes in the organism after the toxin is absorbed? According to my experience, the toxin is not, as a rule, found in the blood during the incubation period, nor in the nerves of the infected locality, after the injection of small quantities of the culture or the toxin. I was able to demonstrate its presence in the blood of mice only after these animals had received proportionately large doses. Curiously enough, it is not found in this stage in the central nervous system, although the nerve cells, according to Goldscheider, have already undergone a peculiar change. After the symptoms had developed as a result of infection, the toxin was frequently found in greater or less amount in the blood of the animal; in many cases, however, it was diminished in quantity, so that it is probably not essential in tetanus that the toxin should be found in appreciable quantities in the blood. Kartner maintains, however, that the presence and amount of tetanus toxin in the blood can be made use of as diagnostic and prognostic signs, as its presence in the blood corroborates the diagnosis and its absence renders a favorable prognosis possible. Roux, however, with justice opposes this view for the reason that in the chronic forms of tetanus the presence of toxin frequently cannot be demonstrated, and yet the patient dies. I have myself observed a case in which 1 cm. blood from a patient in an early stage of a slowly progressing but later exceedingly pronounced tetanus did not prove fatal to mice, the patient, nevertheless, succumbing to reflex spasms. We would do well in regard to this to remember that although the toxin frequently circulates in the blood, as can be demonstrated, this is not necessary to produce tetanus. The toxin in the latter case is probably first carried by the way of the lymphatics of the nerves involved, as I have demonstrated in the case of rabies, and this view is strengthened by the fact of the appearance of the first symptoms in experimental tetanus in the neighborhood of the point of inoculation.

In the human subject, it is true, the susceptibility of certain motor nerve cells outweighs the irritation of the wound and the conduction through its nerves. Here we must evidently take into consideration the saturation of the blood by the toxins, but it must be assumed that this saturation occurs only once or periodically, so that we are frequently, in a given case, unable in our examination of the blood to demonstrate the presence of toxins. If the bacilli, in experimental tetanus, are not demonstrable an hour after infection, the toxin is in all probability present in the blood temporarily. Of great interest in this connection is the assertion, which I am, however, not able to accept in general, that the toxin present in the blood acts, when injected into animals, without any period of incubation. I have observed cases, it is true, in which the symptoms appeared a few hours only after the injection of blood from a patient with tetanus, especially when large amounts were used; but when urine was injected convulsions also appeared in a short time, which could not be attributed to action of the tetanus toxin. The urine, it is true, frequently contains tetanus toxins, but, as a rule, a smaller quantity than the blood. When the blood contained only a small quantity of toxin, the experimental animals sometimes did not show symptoms of tetanus until a number of days had passed. Courmont and Doyon also maintain that the poison circulating in the blood will resist a greater degree of heat than that procured from cultures. This would go to show that the toxin becomes changed in the organism, and there are also other facts in support of this view. Thus, I thought I had found in one of my experiments that the blood of the animal inoculated with toxin contained more toxin, after tetanus had developed, than had been injected, so that the poison must have acted as a kind of ferment, and in this manner a larger quantity was generated by the organism. Here we may also mention the assertion that a substance similar to strychnine has been demonstrated in the brain of animals which succumbed to tetanus. Finally, I have occasionally found the brain of a mouse dead of tetanus to act as a poison in other mice, the latter dying but without tetanic symptoms, and their brains again being poisonous to other mice. How and where does this change of the tetanus toxin into a poison acting in this way take place? We may surmise with some show of reason that this is accomplished by the deposition of the toxin in certain localities which have for it a certain chemical or maybe mechanical affinity. These localities are undoubtedly to be looked for in the place whence the tetanic symptoms take their origin. These are not, as Courmont erroneously believed, the nerve-endings, but the motor nerve cells of the brain and in part also of the spinal cord. The cells of this region already present in the stage of incubation changes which are obviously caused by the action of the poison, and a reaction on their part is induced. In all probability, substances are derived from the cell which combine with the toxin and form a compound which induces the tetanic symptoms. The toxin combines with more and more material from the cells until the blood of the animal, in spite of the progressive course of the tetanus, gradually loses some of its power to induce the symptoms of the disease.

According to this view (Ehrlich, Blumenthal) tetanus is the result of a combination of the cell substance with the toxin, by which, as I believe, the cell is placed in a condition of hyperexcitability; derivatives from the cell are at the same time detached and enter into the circulation, having a tendency also to combine with the toxin.

I have shown that the poison of rabies may be destroyed by the normal nerve substance, as we are able with this to inoculate against rabies. This fact can be explained only by assuming that the toxin of rabies combines in the blood with the nerve substance, and so does not reach the living nerve cells to alter them and produce the symptoms of the disease. Wassermann and Takaki have demonstrated that the poison of tetanus can also, up to a certain degree, combine with normal nerve substance. It is doubtless true that a mixture of toxin with nerve substance may produce a new body, but this possibility was eliminated in my experiments in which I injected the virus of rabies and the nerve substance singly. In one case of trismus in a child, which was, however, already far advanced, I tried the injection of large quantities of normal nerve substance, without any success, however, as the child succumbed in a paroxysm of asphyxia, after a slight amelioration of the tetanic symptoms. It is difficult to understand why the nerve substance is active only when it circulates in the blood before the tetanus toxin has attacked the cerebral cells. After the changes have once developed in the brain the inoculation of cerebral matter will accomplish very little; at most it will prevent newly formed toxin from acting on the brain. In case antitoxin cannot be procured I would recommend the injection in large quantities of an emulsion of lamb's brain in one-half-per-cent. solution of carbolic acid or in cresol solution, as both the brain substance and the carbolic acid answer to the theoretical demands. We shall see later that the antitoxin exerts a therapeutic or prophylactic effect only when it can reach and antidote the toxin in the blood.

Just as in typhoid fever we find substances in the blood which are inimical to the typhoid bacillus, so in other infectious diseases there are certain localities containing antidotal substances. Thus, Franzius found in the bile of animals suffering from rabies, and Koch in that of animals with rinderpest, certain bodies antagonistic to the pathogenic agents of the disease. Lately Tizzoni has also discovered in the bile in tetanus antitoxic substances, which though very weak, could protect mice and guinea-pigs against small doses of the toxin. The action of these substances is, however, altogether too feeble to be of any therapeutic importance. We have in all probability to deal here with certain products of the nerve cells, which have been excreted in the contest with the tetanus toxin, and have then entered the bile. As the liver is also able to destroy the tetanus toxin, we are obviously dealing here with two synergistic substances.

ORRHOTHERAPY.

Richet and Héricourt had suggested that the blood of animals which had passed through an attack of an infectious disease might possess certain curative properties; and following them I was the first, working in conjunction with Lepp, to demonstrate that the blood of immunized animals contains certain substances by means of which other animals may be immunized (1889), and that especially in rabies the blood of dogs which have been made refractory to the disease contains substances by means of which other animals may be protected against the same disease. It is true that this substance does not act after the disease has fully declared itself, for the reason, as has been mentioned above, that the nerve cells are then already damaged, while previous to the outbreak of the disease the anticorpuscles present in the blood do not permit the virus or a part of it to reach the nerve cells, but combine with it in the blood to form an innocuous substance. At the same time it was demonstrated by Charrin and Bouchard that the antidotal substances in the blood are especially contained in the serum. To obtain an antitoxic serum for tetanus, animals must first be immunized against the disease, as was first successfully done by Behring and Kitasato. At the same time I also was experimenting along similar lines. I succeeded in curing animals (rats, rabbits, guinea-pigs, and dogs) of tetanus by means of carbolic-acid injections, and then after various periods of time used the blood of these animals for curative inoculations. Some of the animals were, in fact, made immune against a second infection, after having passed through one attack of the disease; and in the blood of these protective substances made their appearance after a longer or shorter period.

The experiments, made on December 6th, 1889, were as follows: Two rats were inoculated with tetanus, and at the same time treated with carbolic-acid injections. These animals remained immune while the control animal succumbed. Blood from these animals was obtained eight days after recovery, and injected into a young man who was suffering from a grave attack of tetanus following a gangrenous incised and contused wound of the thigh; the result was negative. At the same time two rats and two mice were inoculated with this same blood, after they had, together with the control animals, been previously inoculated with tetanus toxin. One mouse and one rat remained immune. Two rabbits also escaped as a result of inoculation, before and after infection, with blood taken from a rabbit that had been cured by carbolic-acid injections (*Annales de l'Institut de Bactériologie*, Bucharest, 1892). Behring and Kitasato treated filtrates of tetanus cultures with trichloride of iodine or with iodide of potassium solution (Roux and Vaillard) by which means its poisonous action could be progressively and definitely attenuated. A very weak toxin thus prepared made animals immune against a stronger one, and this against still more virulent toxins, until finally large quantities of toxin, or of virulent cultures, could be injected with impunity.

I have frequently repeated these experiments and have found the following order of procedure the best: Six rabbits were inoculated with virulent tetanus cultures to which had been added 0.5 c.c. of an 0.18-per-cent. solution of iodo-trichloride, none of the animals showing any symptoms of infection. Injections were then made as follows: four days later 1 c.c. of the same solution, six days later 1.5 c.c. of a solution containing 0.125 per cent. of iodo-trichloride, five days later 2 c.c. of the same solution, five days later 2.5 c.c., five days later 1 c.c. of a virulent culture, one week later 2 c.c., and one week later again 2.5 c.c. of a virulent culture. A control animal died of tetanus thirty-six hours after the injection of a small quantity of this virulent culture. Rats could also be made immune by this process. At this time a horse was put under treatment for the purpose of supplying antitoxin. The animal was inoculated with 10 c.c. of a virulent culture containing 0.25 per cent. of iodo-trichloride, after three weeks with 5 c.c., and five days later with 10 c.c. of the same mixture. The animal was seized with a temporary stiffness of the back and tail and with trismus, and lost in weight; the temperature rose to 39°. Four days later these symptoms disappeared, the temperature falling to 37.5°. An injection was made of 2 c.c. of a 0.1-per-cent. mixture, after five days 1 c.c. of a 0.05-per-cent. mixture, after four days 0.3 c.c. of a virulent culture, after four days again 1 c.c., and at the end of four days more 1.5 c.c. of a virulent culture. Twenty-two days later an intravenous injection of a virulent culture failed to produce tetanus.

My own, as well as Kitasato's, experiments with cultures attenuated by heating were negative, although the heating of the virus of rabies renders it suitable for immunization. The addition of an iodo-potassium-iodide solution, on the other hand, gives a very serviceable mixture for immunization, and is what I employ at the present time for this purpose.

The method of preparing antitoxic serum in use at the Bacteriological Institute is the following: A horse, five years old, 1.5 metres in height, weighing 461 kgm., is inoculated with a mixture of 0.5 c.c. toxin (of which 0.001 mgm. kills a mouse) and 0.5 c.c. iodo-potassium iodide, and then at intervals of four to five days with 2.5 c.c., 4, 5, and 10 c.c. of the same mixture. After this injections are made of progressively stronger mixtures, at first 2 parts of toxin to 1 of the iodo-potassium-iodide solution, 10 c.c.; then 3:1, 10 c.c.; 4:1, 5 c.c.; 15:1, 10 c.c.; 30:1, 25 c.c.; and finally virulent cultures, in progressive doses of 10, 20, 30, and 50 c.c. One week after the last injection 1 c.c. of the blood of this horse will antidote 50 c.c. of toxin. The injection of toxin is continued and the dose is raised to 200 c.c. The blood of the animal is drawn from eight to fourteen days after the last injection, and the serum of this horse, according to our estimate, contains about ten immunity units in each cubic centimetre. The filtrate of the bouillon cultures was mixed with an equal quantity of common salt, whereby it retained the same height of virulency. In the same manner we have been able to immunize a cow against tetanus, and it was found that the milk was also rich in antitoxin. The same thing has been demonstrated by Rieger and Ehrlich in the case of the goat. Chickens which are able to bear large doses of toxin without any previous preparation yield in time large quantities of antitoxin, so that they can be profitably utilized in the manufacture of antitoxin. Latterly, we are also using successfully toxin neutralized by antitoxin, that is to say, a mixture of toxin and antitoxin, in order to obtain antitoxin from larger animals. We demonstrated in the first place that rabbits, which have received a number of times a safe mixture of toxin and antitoxin, become immune against the poison as progressively less antitoxin and more toxin is injected. After two injections of the mixture, rabbits will bear large quantities of a virulent toxin or culture. If we now inject larger doses of toxin at intervals of four to eight days we very soon obtain a considerable degree of refractoriness to the toxin, and at the same time the formation of a perceptible amount of antitoxin in the blood. In the days immediately following the injection of toxin, the organism becomes somewhat weakened and furnishes less antitoxin than before the injection, but within a few days the production of antitoxin increases above what it was before. The healthier the animal, and the stronger the injected toxin which the animal can bear without suffering from marked debility, the greater will be the quantity of antitoxin manufactured. Unfortunately, however, the production of antitoxin usually becomes diminished with time, after a few years, due to the coming on of a refractory condition, analogous to natural immunity, as the animal cannot be infected any more by tetanus and no longer produce the slightest amount of antitoxin.

We have already seen that the organism contains antitoxins against various infections. These exist in parts already formed in the normal organism, and their presence serves to explain in a measure the phenomenon of natural immunity; other antitoxins are formed in certain parts of the organism during the course of an infectious disease, and still others are formed at the expiration of an infectious disease. Tetanus antitoxin belongs to the latter category. It represents in all probability that substance which while forming a part of the normal nerve cell, is at the same time a means of protection against noxious matters. It is not by any means a product of the tetanus bacillus, as Rieger, Roux, Metchnikoff, and others believe, as it may be produced in the presence of toxins without bacilli. It is certainly not present in the toxin itself, as I have treated and destroyed large quantities of toxin with heat and carbolic acid without being able to produce antitoxin from it.

According to Ehrlich antitoxin is the substance which combines with the toxin in the nerve cell itself to form the real tetanus poison. I think that we are at present not justified in accepting so simple an hypothesis. In the first place we are not compelled to assume the existence of a specific tetanus poison. It is sufficient that the nerve cells are changed in such a manner by the toxin that they acquire a peculiar hyperexcitability, which gives rise to tetanus. Our methods of investigation do not permit us to determine whether with this there is present a poisonous substance in the cell, or rather whether certain constituents of the cell substance which regulate its function have been peculiarly changed or perhaps destroyed or removed. As regards the formation of antitoxin we may probably assume that it is formed at the point where the toxin acts on the organism, namely, in the central nervous system, although it cannot be demonstrated here in larger quantities than in the blood. But this is accounted for by the fact that the blood washes out the formed antitoxin and retains it in solution. My explanation of the formation of antitoxin is similar to that of Ehrlich, namely, that it is formed by the resistance of the nerve cell to the attack of the toxin; the cell, as a result of repeated attacks, forming and excreting an excess of protective material which circulates in the blood. It seems probable that not only the central nervous system wages war on the toxin of tetanus, but also other organs and secretions, which during life may injure the toxin, as the bile, the liver, and especially, as has been shown by Brieger, Kitasato, and Wassermann, the thymus gland. The intraperitoneal injection of a mixture of tetanus toxin and thymus extract is sufficient to render animals, especially rabbits, mice, and sheep, immune to the toxin and cultures. As follows from the most recent teaching, the explanation of this is not that the thymus extract destroys the poisonous substances of the bacteria, allowing the immunizing substances to escape, but merely that the thymus extract attenuates the toxin, which is now unable to act on the organism by producing tetanus, but only stimulates the more copious formation and excretion of the anticorpuscles.

The antitoxin has been frequently examined chemically, but so far nothing has been demonstrated except that (1) it does not in all probability represent an albuminoid body; (2) it is only with difficulty filtered; (3) it is rich in phosphorus; (4) it is not destroyed below the temperature of boiling water, and is therefore more stable than the toxin; (5) it does not exert a direct irritation on the organism; (6) it is not changed by the action of carbolic acid; (7) it is precipitated by alcohol.

This does not, however, prove that antitoxin is altogether non-poisonous. The antidotes, especially of the alkaloids, as we know, are as a rule poisonous. Any antitoxin is to a certain extent antagonistic to disease, as only animals which are perfectly healthy and strong produce it, and if they become ill or weakened, the amount of antitoxin in the blood is rapidly reduced. Nevertheless, the cases of disease following chronic infection, as in syphilis, in which the syphilitic virus is no longer present although the subjects are immune against a new infection, seem to speak in favor of the fact that such sequelæ may be dependent upon the action of the same substances which occasion the immunity. At all events, nothing of this kind has yet been noticed in man after the use of antitoxin. I have, it is true, killed rabbits by injecting large quantities of antitoxin, and noted in them cachectic symptoms during life and changes in the nerve cells after death; but when we think how much antitoxin circulates in the blood of our serum animals for years, and how healthy they are withal, we shall be cautious in arriving at a premature generalization from these experimental results. The explanation of them, indeed, is not difficult to find. We may simply assume that though robust animals may manufacture certain quantities of antitoxin, retain them in the system, and thrive, this same antitoxin will have a deleterious effect if the animal becomes debilitated from any cause, for the reason that then the formation of fresh antitoxin is arrested. The antitoxin of a robust animal may very well exert a poisonous influence on a weaker animal or on one of different kind or constitution.

To judge of the action of antitetanus serum, we must try to determine its strength by means of a test toxin, that is to say, a toxin whose strength in the fresh state is known. Unfortunately, however, the toxin of tetanus is, as we have seen, not very stable, so that it must be repeatedly examined. If the minimum dose of the toxin which kills a mouse is rated at 0.5 mgm., a serum of 1:1,000,000 would mean that 0.01 mgm. of this serum would be sufficient to protect 1 gm. weight of mouse from the minimum dose of the toxin. The amount of this serum necessary to immunize a horse would be about 0.25 gm. For the cure of a case of tetanus one thousand times the amount of the immunizing dose would be necessary; thus for a human subject 100 gm. of a serum 1:1,000,000, about 10 gm. of a serum 1:10,000,000, or 2 gm. of a serum 1:50,000,000. This serum is taken from the horse, like the diphtheria antitoxin, about eight to fourteen days after the last injection, by means of a sterilized cannula and aspirating syringe, and placed in the ice-box in large demijohns for coagulation; then the serum is carefully removed, mixed with 0.5 per cent. of carbolic acid, and one per cent. in volume of chloroform, when it can be kept for years (having now become very durable) in well-closed bottles in the dark. I have found, however, that the serum occasionally loses its strength rapidly without any assignable cause, so that it can by no means always be relied on.

Behring thought himself justified in assuming that the mortality of tetanus would be reduced from eighty-seven per cent. to about twenty-five or thirty per cent. by means of the serum. The reason for this belief is, however, not very clear to me, as we are able to effect a cure in experimental animals only under certain conditions. As we have seen, the results obtained in the prevention of an outbreak of this disease, especially among horses and cattle, are much more encouraging. In mice as well as in larger animals we have been able, by means of our serum, to prevent altogether the occurrence of the disease if treatment was begun a few hours after infection, and to cure the animals after infection by toxin, if given at the onset of the attack, in small doses. But like Brieger and Kitasato, I have been unable to save the animals even with very large doses, when infection had taken place by means of splinters which contained the spores of tetanus. Immunization also could be obtained only in rare instances when infection was produced by spore-laden splinters. As now tetanus in man is in most cases due to an infection with splinters, not much is to be expected from the antitoxin in these cases. Undoubtedly there are also cases in man in which the bacillus of tetanus soon disappears from the wound; but the experiments bearing on this are open to objection, for the reason that when no bacilli are found in the wound it is probable that they are hidden in some undiscovered places. At all events, the conditions which are encountered in experimental tetanus will in all probability only rarely be realized in natural infection. We very rarely meet with tetanus in man produced by a pure culture of the bacillus without spores, and more infrequently still a pure tetanus intoxication, but these are just the cases in which the tetanus antitoxin is effective. Theoretically, it is easily explained why infection by splinters is so difficult to cure by antitoxin. From the splinter, under favorable surrounding circumstances, progressive cultures of bacilli will be formed, and of their products a part will undoubtedly be neutralized in the blood by the injection of antitoxin; but this injection will have no influence on the tetanus culture. If, as is the case in experimental tetanus, the bacilli could be destroyed in a few hours, the evil would certainly be eradicated; but this is not the case here, as the splinter or foreign body always contains spores and bacilli which are protected from the action of the organism. Indeed, I was able to pass splinters which had caused tetanus in man through a long series of animals (guinea-pigs and mice), the same splinter repeatedly causing tetanus which could not be arrested by antitoxin. Only in rabbits they failed to cause tetanus, but did not lose their virulence in respect of other animals. In frogs, on the other hand, they failed to induce tetanus, but then lost their poisonous effects on other susceptible animals. According to this the frog in its normal condition possesses, besides its low temperature, some peculiar property which destroys the tetanus spores, and which property becomes powerless when the animal is warmed.

It is important that the antitoxin should be as fresh as possible and should be injected in as large a quantity and as frequently repeated as is feasible, in order that the toxins which are yet circulating in the blood may be destroyed, for after they have once excited an undue irritability, tetanus will occur. In such a case there is probably mainly a vicious distribution of the molecules within the cell, in consequence of which the action of the antitoxin seems nil. In this case there will have to be a regeneration or change in the altered portion of the cell to effect a cure. As, however, according to the results of my experimental researches, individual cells only are affected in certain cell groups, fresh quantities of toxin will affect the rest of the intact cells, increasing the tetanus, and the antitoxin will be serviceable in neutralizing the fresh amounts of toxin. We have of course only an imperfect idea of the amount of toxin which, in a given case, may circulate in the blood, and accordingly we are somewhat at a loss to determine the proper period for the injection, as well as the amount of the serum necessary. Behring's calculation of the necessary amount of antitoxin is of very little value in the treatment of human tetanus. I believe that it is proper to inundate the organism continuously or very frequently with large quantities of antitoxin, but this, in view of the high price and the difficulty of manufacture of the serum, can hardly be carried out.

The serum exercises its effect for a few days only, as the antitoxin is rapidly eliminated. For this reason I have attempted to render the action of the remedy more positive, by injecting together with the antitoxin certain increasing doses of toxin. The toxin, as we have seen, is certainly able, in increasing doses and mixed with antitoxin, to immunize the organism against tetanus, an effective and permanent immunity instead of the temporary one obtained by antitoxin. Unfortunately, however, the grave tetanus cases run such a rapid course that we cannot expect great results from a gradual immunization. In several cases I have seen more favorable results when using injections of iodo-potassium iodide or carbolic acid, during the intervals of antitoxin injections, this practice being based theoretically on the antidotal action of carbolic acid and iodine on the tetanus toxin.

As a general thing I have used antitoxin in larger and more frequently repeated doses than any other of whom I have knowledge, always using 300 to 500 c.c., and I have also achieved fairly good results.

It is not a matter of indifference in what part of the body antitoxin is injected. The nearer it is injected to the brain or to the threatened nerve cells, the more assured is the probability that it will be able to prevent the toxin from attacking these. The path from the wound to the brain naturally varies in length in different cases. I was the first (later Roux and Nocard corroborated me) to demonstrate that when the toxin is injected into the brain of the animal, tetanus makes its appearance much more rapidly, and, according to Roux, with peculiar symptoms of cerebellar irritation. According to my experiments in 1890 a fatal tetanus occurs after subdural injections in rabbits in about twelve hours, being manifested by symptoms of irritation, a temperature of 40° C., increased respiration, and convulsions within forty-eight hours. I was able, however, to demonstrate the presence of muscular rigidity, as in ordinary tetanus. According to Roux and Borrel (International Congress of Hygiene at Madrid, 1898) this cerebral tetanus is characterized by epileptiform convulsions, twitchings, and polyuria, while ordinary tetanus is characterized by the tonic muscular contractions.

An animal, immunized by antitoxin injections against ordinary tetanus, is, according to these authors, not immune against cerebral tetanus. We are not justified in concluding from this that the antitoxin injected subcutaneously does not reach the cerebral cells, for otherwise the initial stage in all forms of tetanus would not be amenable to a cure by this method. The only correct deduction is that when the serum is hypodermatically injected such a small quantity of antitoxin reaches the brain that it is unable to antidote the effect of the direct injection of toxin. Out of forty-five guinea-pigs and rabbits which had already shown some symptoms of tetanus for a period of twenty-four hours, thirty-five were cured by the intracranial injections of antitoxin. When the symptoms were not too violent we were able sometimes to cure animals with cerebral tetanus by the usual method. Roux and Borrel, under similar conditions, saved only two out of seventeen. At all events, the injection into the brain is more advantageous than the subcutaneous method. The experiments do not, however, prove that the antitoxin is not formed in the brain, neither that the cerebral cells cannot be immunized. The toxins, it is true, are prevented by the antitoxin circulating in the blood from reaching the cerebral cells, but the fact of the more rapid immunization and cure in cases of cerebral inoculation indicates that the cerebral cell forms the point of attack for the toxins, and as soon as it was demonstrated that the cell resisted the toxin and that only the normal cerebral substance contained antitoxic material, the manufacture of antitoxin on part of the brain not only could not be denied but even became quite probable. Metchnikoff attempts to explain the effect by the accumulation of leucocytes and destruction of the tetanus toxin by them, but this is an hypothesis which is contrary to all experience in tetanus, since inflammation and irritation caused by the bacillus itself usually lead to an attack of tetanus accompanied by an accumulation of leucocytes, but they do not prevent the attack. If we find injections of brain matter active some time after infection, this can hardly be attributed to the accumulation of leucocytes.

Tizzoni (*Gazzetta degli Ospitali*, March, 1898) claims that he is able to overcome tetanus by means of injections of pneumococcus cultures. The action of the cultures is said to be exceedingly rapid, and is due to the similarity of the tetanus toxins to those of pneumonia. This effect might possibly, however, be explained by the leucocytosis caused by the pneumococcus. The results of experiments concerning cerebral tetanus led Roux and Borrel to resort to intracerebral injections of antitoxin. After trepanning over the region of the psychomotor centres, they injected the antitoxin in this region, with the result of a gradual recovery in the animals experimented upon. These experiments were not made, it is true, in tetanus caused by splinters and in advanced cases of the disease.

Obviously this method is preferable to that of subcutaneous or of intraperitoneal injections, which have given few successful results up to the present time. The essential objections to the effectiveness of the antitoxin method in certain cases of human tetanus are not wholly overcome by the scanty results of intracerebral injections. Even when this method is resorted to the symptoms do not always remain stationary, and the results are not always absolute or absolutely convincing. According to Roux and Borrel, a cessation, an "immobilization" of the process, is noted after intracerebral injections, and if the disease is not already too far advanced, this will gradually if not immediately pass on to recovery. Just as cerebral irritation is produced in animals by intracerebral injections of tetanus antitoxin, this occurred also in the few cases in man. The injection first produced a focus of softening, which was followed by cardiac debility and tachycardia, which, however, was merely temporary in two cases, then finally psychical excitement and mental disturbance, which also disappeared without leaving a trace. The gravity of these symptoms would lead us to resort to cerebral injections only in the most severe cases. Curiously enough the cases on record in which this method of treatment has been employed are not described in such a manner that we are able to judge fairly of the gravity of the case. Before we can properly estimate the value of the serum treatment of tetanus we must have detailed reports of a large number of cases, especially of those in which all the characteristics of a grave and nearly always fatal form were present, that is to say, cases in which violent trismus occurred within the first week after the injury. It must be said of the cases up to the present time that different men have worked with serum of varying strength and in varying, often insufficient, doses. The most extensively used preparation is probably that of Behring. This can be obtained both in the fluid and in the dry form. The dry preparation contains 500 units in 5 gm. This amount should be dissolved in 45 c.c. of water at a temperature of 40° C. The new liquid preparation is put up in bottles each of which contains 25 c.c. of serum, the contents of two bottles having 500 units. This dose should be injected as soon as possible after the appearance of the symptoms. For children half the quantity is sufficient, namely, 25 gm. On the following days the injection is to be repeated with half the dose. The antitoxic serum of Roux and Vaillard is, according to our experiments, of about equal strength, while that which is prepared in our own institute at Bucharest is about one-half as strong, and the preparation sent us by Tizzoni and Cattani is about fifty times weaker. Besides this, preparations are made by the British Institute of Preventive Medicine, also by several manufacturers in America and England.

The serum, just as in the case of diphtheria, is injected with all antiseptic and aseptic precautions. I employ a syringe holding 30 gm., which is first sterilized by boiling; when injections are to be given on several successive days, it is sufficient to wash the syringe with hot distilled water, alcohol, and a three-per-cent. solution of carbolic acid. The cannula is sterilized by immersing it in oil heated to 150° C. The skin is sterilized by scrubbing it with alcohol and corrosive sublimate. The lower part of the back of the neck is to be recommended as the place of injection. I apply a light cotton dressing over the point of injection. Sometimes the injection is followed by a temporary diffuse papular erythema accompanied by a slight general nervous disturbance. Over 400 gm. of serum have been injected by me within four days, without any bad results, in a number of cases. Behring's view on the dose to be administered in man in individual cases seems to me, as we have seen, incorrect, and I cannot sufficiently lay stress on the advantages of injection in the most rapid manner of large doses of the most concentrated serum. Thus we find in the case of diphtheria in Bucharest, where we administer about double the dose of antitoxin, that our statistics show noticeably better results than those from foreign countries.

Let us endeavor now to determine what results from antitoxin treatment we may expect, according to the gravity of the case. In the first place we look for recovery in those cases in which the disease makes its appearance one week after the injury and is fully developed within forty-eight hours. To this category belong the cases of Roux and Vaillard, Douglas, Bruns, Lund, and Erdheim, which ended fatally; only one case of the kind, that of Weischer, seems to have recovered, which would give us one cure out of ten cases. Treatment by antitoxin can therefore hardly be regarded as effective in these very grave cases.

In other somewhat less grave cases on the other hand, which previous statistics have shown to have a mortality of 88 per cent., the treatment with antitoxin seems to have afforded better results. According to Heddaeus the mortality in 98 cases of tetanus after treatment by antitoxin was 41.8 per cent., which would mean a reduction of about one-half. It is true that many light cases were included in these statistics, and other remedies were also used besides the antitoxin. We also cannot deny the fact that many cases in which death followed the injections of antitoxin were not published, so that Heddaeus' statistics are to be accepted with great caution.

In this relation, the reports of cases in which Tizzoni's antitoxin was employed are most instructive.

Between 1891 and 1893 I collected ten cases, which were treated by Tizzoni's antitoxin. In the greater number of these cases the amount injected was from 1 to 2 c.c.—an altogether insufficient dose, and in spite of this nine recoveries out of ten cases were reported. Here obviously the fatal cases have not been published, for even when doses of several hundred cubic centimetres of a stronger antitoxin were employed the mortality was over thirty per cent.

In Wagner's latest collection of cases we find thirty cures and sixteen deaths, a mortality therefore of about thirty-five per cent. We have no reason to suspect that many of the fatal cases were not included in these statistics.

My own experience with antitoxin treatment is covered by seven cases, one of which probably represented the gravest form. A gardener suffering from a deep wound of the foot, soiled with dirt, was taken on the eighth day with marked trismus, and on the third day of the disease there were complete stiffness of the spinal column, involving the muscles of the arms, rise of temperature, and frightful respiratory and reflex spasms. The patient received an injection on the first day of 40 c.c. of our serum obtained from an immunized cow, and on each of the following three days one of 60 c.c., receiving altogether in nine days 380 c.c. Marked erythema appeared, but there was a surprisingly rapid improvement followed by recovery. On the following day a new case occurred in the same institution in the person of a hostler with deep, small fissures in the skin of the soles of the feet, with dirt and slight ichorous suppuration at the bottom of the wounds. There was complete trismus with opisthotonos on the fifth day, aggravated by reflex spasms, and a rise of temperature. Daily injections of serum were given, the man receiving in eleven days 405 c.c. of the Bucharest serum. A perfect cure was obtained in seventeen days. In a third less severe case, cure was obtained with 320 c.c. of antitoxin in ten days. In a fourth case presenting total trismus and opisthotonos with frequent spasms, the disease had developed gradually, infection having occurred through erosions on the feet. On the eighth day injections were begun and were continued twenty days, altogether 360 c.c. of serum being used. As a result of the serum injections, a constant improvement in the symptoms was observed, the temperature fell, and a marked relaxation of the muscles in the neighborhood occurred, as well as a great improvement of the general condition. Recovery took place at the end of thirty-two days, although a very noticeable stiffness of the lower extremities remained. At the end of three weeks there was a slight relapse. The fifth case was a severe one in which the disease developed eight days after the injury. The symptoms were complete trismus, opisthotonos, and muscular spasms. Each injection of serum was followed by marked improvement, and a cure was obtained in twenty days, after 260 c.c. had been employed, only a slight stiffness remaining. In contrast to these results was one case of well-marked gangrene of the thigh following a contusion, in which death occurred, nothing having been done for the wound nor any kind of operation undertaken. Four other patients suffering with tetanus who contracted it at the same time, and were not treated with antitoxin, succumbed to the disease.

As regards the activity of the various serum preparations, my impression is that the Paris product gives especially good results. Our own preparation also, which according to our experiments is about one-half as strong, gave very good results in my hands, after I began to use it in larger doses than others had done before. I can truly say that our serum administered in large doses has given the best results hitherto obtained. The later preparations of the Paris serum, according to the sources to which I have access, have given something below forty per cent. of cures, while Behring's preparation gave about the same percentage or maybe a little higher. During the present year three cases of tetanus have been treated with intracerebral injections of antitoxin after the method of Roux and Borrel. Two patients recovered, while one died in spite of this treatment. The first case was evidently a grave one, but not of the most severe type. The symptoms were distinctly marked five days after its commencement, trismus and opisthotonos being present with acceleration of the pulse. The skull was opened by a trephine 8 mm. in diameter applied over the foot of the second frontal convolution, and several cubic centimetres of antitoxin were injected. The contractions seemed to become "fixed," so to speak, by the injection and then gradually disappeared. But as trismus and opisthotonos were present, it is difficult to judge whether the injection "fixed" the spasm; at all events it was not followed by rapid improvement. Tachycardia, mild delirium, insomnia, and oliguria increased, and only on the seventh day after the injections had been commenced improvement gradually took place. A very grave case ended fatally, and in a third case which developed gradually a cure was again obtained. In the last case 116 c.c. of serum was also injected subcutaneously in addition to the intracranial injection. This latter case proves even less than the first the superiority of this procedure, which as we have seen causes temporary psychical disturbances and a focus of softening in the brain. Theoretically, it must of course be assumed that the injection of antitoxin into the brain will have a more rapid and concentrated effect than if the serum is subcutaneously or intravenously administered. We are able to cure animals with greater certainty by trephining than by subcutaneous injection, but in natural tetanus other factors are present which exert great influence on the activity of the antitoxin. As a matter of fact, two further cases of intracerebral injections have very recently been reported, and to these I may add a personal observation, all three of which ended in death; in two of the cases the symptoms, especially the contractions, increased in extent and intensity after the injection. As an explanation of these symptoms as well as of the complications which occur after the intracranial injection in man, we should perhaps take into account the bacterial association, the susceptibility of the human brain, and also the repeated entrance into the circulation of large quantities of toxin, which does not take place after the antitoxin has been injected into the circulation.

In conclusion, we may say that the treatment with antitoxin as well as its intracranial injection must be looked upon as a marked advance, but it should not restrain us from making use of other well-tried remedies.

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CANCER.

(GENERAL PATHOLOGY.)

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CANCER.

(GENERAL PATHOLOGY.)

Introduction.

The term "cancer," after having in the past undergone repeated changes of meaning, is now used in such different senses that it is necessary for those who employ it to state precisely what they mean by it. In the popular sense, every malignant neoplasm is a cancer. In medical science, however, the term is usually restricted to certain malignant neoplasms, *viz.*, to those of *epithelial* origin; and this is the sense in which I employ it. This view of the origin of cancer, which we owe chiefly to Waldeyer and Thiersch, has replaced the older doctrine of the connective-tissue origin of the disease, as propounded by Virchow and his followers. Even Cornil, who for so many years ably upheld the latter doctrine, is now convinced of its error. Hence we must look to preëxisting epithelial cells for the germs whence cancers arise. It is necessary to insist upon this, because some modern pathologists (Ruge and Veit, Ribbert, and others) still uphold the ancient doctrine. By Virchow the connective tissue was regarded as an indifferent matrix, whence, under certain conditions, any tissue might arise (*metaplasia*). This doctrine ignores the specificity of the tissue elements which embryology has revealed. In the normal ontogeny, a derivative of one germ layer never develops a structure originally derived from another; thus epithelial elements always remain within their own type and never originate connective-tissue structures, and *vice versa*. In fact, after the differentiation of the blastodermic layers no wholly indifferent cells are ever formed; that is to say, no cells are formed like those of the morula, whence any structure may finally develop. Cells subsequently arising can only develop certain tissues, *viz.*, those which are normally derived from the germ layer whence they originate. In the development of pathological new formations the same law is observed. There are among neoplasms no transitions from one specific tissue type to another; in short, the metaplasia of Virchow does not exist.

Cancers are almost invariably "pure" tumors; that is to say, their *essential* elements all belong to but a single tissue type—the epithelial;

it is most exceptional to find other tissue types (cartilage, bone, etc.) represented in their structure. Hence it may be inferred that the disease rarely arises in connection with embryonic developmental anomalies.

Briefly stated, the chief features of cancer are as follows:

The disease begins as a small, solitary nodule, which, as it increases, interpenetrates the surrounding structures, and eventually completely destroys them.

It has a power of persistent increase, which nothing can stop. Slowly and steadily, but relentlessly, it invades wider and wider areas—regardless of the requirements of the part and of the organism as a whole. Moreover, the disease is malignant. I have observed that some confusion exists as to the precise meaning of this term.* It can hardly be maintained that the essence of malignancy lies in the mere power of persistence and the abnormal proliferative process, as I was once inclined to believe, for this is a property common to all tumors, malignant and non-malignant. It is rather in the properties known as "dissemination," and its consequence, "recurrence," that the essence of malignancy is comprised. The disseminativeness of certain neoplasms is, however, largely of the nature of an accidental occurrence; that is to say, it is chiefly dependent upon local structural peculiarities, which render it easy for the constituent proliferous cells to get access to and to be transported by the adjacent lymphatics and blood-vessels. This explains the great variability in the degree of malignancy that is so frequently witnessed. Moreover, it explains "recurrence" and its variability; for, as we learn from recent operative experience, but for local dissemination—chiefly of the latent kind—malignant tumors would be as easily curable by operation as their non-malignant congeners.

As the disease progresses, a noticeable tumor is after a time formed, which grows and is nourished like a normal part of the body. Yet, in return for the nutriment thus supplied, it contributes nothing serviceable; functionless and redundant, its relationship to the rest of the organism differs but little from that of parasitism.

It is a peculiarity of cancerous tumors that they are less stable than normal parts; moreover, they seldom attain very large size. This is owing to the supervention of degenerative changes, which usually eventuate in intractable forms of ulceration, whence deep, spreading excavations result.

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* The term itself is a relic of the superstition of the Middle Ages, when it was applied to certain intractable diseases, under the belief that these were due to the special influence of malign or evil spirits.

Such is the great tenacity of life and the wonderful proliferative power of even the most diminutive fragments of cancer; that when any of these are left behind after operation—as is usually the case—they only too frequently constitute fresh centres of disease. In this way most of the phenomena of "recurrence" may be explained.

Another remarkable property of cancers is their power of dissemination, whereby new and independent growths similar to the primary one spring up in parts having no direct continuity with the original disease (adjacent lymph glands) and in quite remote parts (liver, lungs, bones, etc.).

Left to itself, cancer almost invariably ends in death. As the disease progresses the patient's health becomes seriously impaired, cachexia supervenes, and after a variable period—usually of from one to five years—death ensues from asthenia.

Historical Review.

We learn from the works of Hippocrates that even at this remote period medical men were acquainted with the cardinal features of cancerous and other tumors; which seem then to have been much the same as they now are. The disease is, therefore, of great antiquity. By Galen and his followers the tumors "*præter naturam*"—which comprised all that we now include under the term "tumor," and many other conditions besides—were believed to result from the accumulation of one or other of the various humors, each of which generated its corresponding kind of tumor. Of these humoral tumors, those of the group called "*scirrhus*"—which embraced cancer, and nearly corresponded with what we now understand by the word "tumor"—were believed to arise from the accumulation of atrabile ("*cancer ab atrabile*").

Many long centuries of stagnation and black superstition elapsed before the doctrine of the humors was overturned by the discovery of the circulation of the blood early in the seventeenth century (Harvey, Malpighi, Leeuwenhoek, and others).

In place of the humors, the blood was now regarded as the true source of the disease.

Early in the eighteenth century the Cartesians, with Boerhaave at their head ("*morbus est vita præter naturam*"), ascribed the origin of all tumors to the newly discovered lymph—a derivative of the blood. Cancer they regarded as the outcome of vitiated, depraved, or degenerated lymph.

Doctrines of this kind continue to hold the field until the time of Hunter (1728–93). With his advent we begin to discern the first rudiments of modern conceptions emerging from the ancient chaos. By studying the structure of tumors, Hunter recognized their affinities with the normal tissues; whence he maintained they arose by a modification of the formative process. This was a great advance on previous ideas. He thus laid the foundations of the anatomico-pathological study of tumors, which were subsequently strengthened and extended by Bichât, Laënnec, Abernethy, Cruveilhier, and others.

At this juncture, early in the nineteenth century, the current of thought was suddenly interrupted and changed by the appearance on the scene of the impetuous Broussais. His doctrine was, that all tumors, including cancers, were but forms of chronic inflammation consequent on organic irritation. The extreme simplicity, comprehensiveness, and positiveness of this brilliant generalization—suddenly sprung on a scientific world, hesitating between the old humoral doctrines and the nascent anatomico-pathological tentatives—captivated every one, and the Broussaisian system became supreme in an incredibly short time. But its supremacy was short-lived.

What more than anything else contributed to its downfall was the application of the microscope to the study of living things. To this instrument and its revelations we are indebted for the two great doctrines of modern medical science—the cell theory and the germ theory. The far-reaching importance of the revolution thus effected is even now by no means duly appreciated. It might be thought that the history of the invention of an instrument, which has done so much to enlarge the field of knowledge as the microscope, would be a theme for every one; but, as a matter of fact, the discovery is shrouded in obscurity. It is believed that the earliest compound microscope was made by Jansens, a spectacle-maker of Middleburg in Holland, near the end of the sixteenth century. One of his instruments was exhibited in London, by Drebbel of Alkmaar, early in the seventeenth century (1617). Unfortunately it was impossible to see clearly with this instrument, when high magnifying powers were used, owing to the disturbing influence of chromatic and spherical aberration; hence the compound microscope was at first merely a scientific toy. It took more than two centuries to overcome these defects. At length, early in the nineteenth century—thanks to the skill of Selligues, Chevalier, Lister, and others—these difficulties were surmounted. In 1830 a really serviceable compound microscope was at last produced; and with its aid naturalists shortly afterwards began to explore the minute structure of organic forms, as Newton had long before predicted. Thus the science of histology was born, which subsequent improvements in optical appliances and a better technique have advanced to its present remarkable state of perfection.

With this new aid the cellular structure of organized beings was ere long discovered. For the famous *Cell theory*—which must be ranked among the most important steps by which the science of biology has ever been advanced—we are indebted to the vegetable morphologist Schleiden; and shortly afterwards Schwann demonstrated the applicability of his generalizations to the animal world (1838). In the very same year the publication of Müller's important work on the origin of tumors established the cellular nature of cancer and other neoplasms. Modern conceptions as to the pathogenesis of tumors date from this period.

Müller believed that the constituent cells of tumors were derived from a formative fluid exuded from the blood (*blastema*); which was nothing but the "coagulable lymph" of Hunter under another name. He ascribed the origin of cancer and other neoplasms, and their variations *inter se*, to aberrations of the force inherent in this primordial substance, causing the resulting cells to deviate from their usual evolution. Müller strongly insisted on the correspondence between the development from the embryo and the pathological neoplastic process. "It is one and the same power which, being maintained continuously from the germ to the latest period of life, determines all organic formation."

Pathological cells, he maintained, differed from physiological cells only in respect to the degree of evolution ultimately attained. The division of neoplasms into two great classes, according as their structure resembled normal tissues (*homologous*), or differed from them (*heterologous*), Müller completely rejected. "It is evident," he says, "that no division of pathological structures into homologous and heterologous can be established. Such a classification is formed without any knowledge of the structure of morbid growths and is founded on blind, gratuitous hypothesis. The most innocent growths do not differ in their minute elements, nor in their origin, from the most malignant ones."

The establishment of the cell theory gave an immense impetus to pathological histology, and a vast mass of new data soon accumulated. These Virchow, twenty years later (1858), pounced upon; and with wonderful insight, skill, and energy he elaborated them—together with independent observations—into a kind of new cell theory, which still prevails. Virchow's influence on modern conceptions has been so great that it will be necessary to trace the genetic relationship of his ideas with those of his predecessors. It may be said that he adopted the cell theory in its entirety, as laid down by Müller, with the single important exception that he completely exorcised the blastemal origin of cells. It was just this omission that chiefly constituted the novelty of his system. Instead of a hypothetical blastema he substituted the famous formula "*omnis cellula e cellulâ.*" "Where a cell arises, there a cell must have previously existed, just as an animal can only spring from an animal, and a plant only from a plant." The doctrine of continuous cellular development, that had been established by Remak for the normal tissues, thus became the basis of Virchow's neoplastic pathogeny.

Another important respect in which Virchow's neoplastic pathogeny differs from that of his predecessors, is in the addition to it of the whilom extinct Broussaisian doctrine of irritation and chronic inflammation. Nowhere in his works have I met with any attempt to explain the compatibility of this view with the doctrine he has also adopted of the correspondence between the embryonic and neoplastic developmental processes. In my opinion, these views are absolutely incompatible; and this incompatibility constitutes a serious flaw in Virchow's neoplastic pathogeny.

Of late, owing to a variety of causes, Virchow's doctrines have undoubtedly lost ground. For this lapse, Virchow himself is to a large extent responsible; because he has gone out of his way, in a really extraordinary manner, to prevent his followers from assimilating the new facts and principles brought to light by modern biological progress in connection with the doctrine of evolution. Hence, while the rest of biology has been revolutionized, the cellular pathology has remained stationary. So far as the pathology of neoplasms is concerned, in my work on "The Principles of Cancer and Tumor Formation" (1888), I endeavored to repair Virchow's error by laying the foundation of a modified cellular pathology in harmony with modern biology; and I confidently look forward to the time when these views will be generally accepted as the only really scientific basis for explaining the phenomena of pathological neoplasia. To this end nothing will be more conducive than the wider spread of biological knowledge among pathologists.

Another circumstance that has tended to weaken Virchow's authority is the large measure of success accorded to a modification of the cellular theory propounded by Cohnheim, according to which the *only* cells of the body capable of originating neoplasms are those contained within certain detached fragments of the various tissues, organs, etc., sequestrated during embryonic life. That a considerable proportion of malignant and non-malignant neoplasms actually do arise in connection with such sequestrations I have convinced myself; but it seems to me in the highest degree improbable that these are the *only* cells capable of originating such growths. On the contrary, as I shall presently show. there are good reasons for believ-

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ing that neoplasms may arise wherever undifferentiated cells are present, and that they are most prone to originate where such cells most abound.

But what, more than any other recent occurrence, has undermined the authority of the cellular neoplastic pathogeny is the widespread belief that neoplasms will eventually turn out to be of *microbic origin.* In short, it is evident that out of the confusion of a transition period, but two conceptions as to the origin of neoplasms have emerged—the one based on the cell theory, and the other on the germ theory; and henceforth the struggle must be between these two.

PATHOGENESIS.

Briefly stated, the question now is: Do cancers and other neoplasms arise, as Johannes Müller believed, through a modification of the formative process; or are they the outcome of the inflammatory process, as Broussais maintained, owing to the intrusion of microörganisms or other irritants *ab extra?* In other words, are they essentially of *intrinsic* or *extrinsic* origin? I incline to the former alternative. I believe that neoplasms arise mainly from the abnormal play of forces generated within the body; and I think the future will see a decided reaction in this direction.

Nobody nowadays thinks of wasting his time in discussing the obsolete riddle as to whether these diseases are of constitutional or local origin. The absurdity of approaching the subject from this standpoint was well shown when, in the course of the celebrated debate at the London Pathological Society (1874), the witty Moxon put this trenchant question, "What can be more constitutional than one's great toe?"

A striking feature about cancerous growths is the great morphological difference that obtains between them, according to the localities whence they originate. What, for instance, can be more divergent in this respect, than the appearances presented on microscopical examination, by sections of cancers from such different parts as the breast, the stomach, and the skin? We learn from such examinations that cancerous growths are sufficiently organized to present unmistakable histological resemblance to the structures whence they originate. Herein they differ completely from the inflammatory pseudoplasms, which present the same indifferent structure, no matter in what part of the body they arise.

Another remarkable property of all cancers is their power of autonomous growth and development (individuality) upon which their so-called parasitism depends. It is by virtue of this property that they tend to persist and increase indefinitely. Nothing comparable to this is seen in connection with inflammatory pseudoplasms, which tend to disappear.

The great resemblance always noticeable between primary and secondary cancerous growths is a phenomenon of similar import, which cannot be accounted for on the basis of inflammation and microörganisms. It is impossible to conceive a valid explanation of such conditions, without the presence of epithelial cells, capable of reproducing their like by growth, multiplication, and organization. I am aware that the microbists affect to make light of this objection, alleging that the emigrant cancer cells carry their parasites with them to their new habitat, where the said parasites cause a repetition of the initial morbid process. It never seems to have occurred to the authors of this feeble suggestion, how unlikely it would be for microbes transported to the liver, to produce in this organ the typical structure of breast cancer. Surely, if the secondary lesions were really due to microbes, these would infect the liver cells, and so cause the formation of typical hepatic cancer. In short these phenomena evidently imply that the disease centres in the epithelial cells themselves.

Such are some of the reasons for regarding the theory of irritants *ab extrâ* as improbable.

The results of statistical researches as to the connection between traumata, preëxisting disease, and the outbreak of cancer, are of similar import; they show that in the great majority of cases the origin of this disease cannot be attributed to the immediate action of any appreciable extrinsic cause whatever. But of this more anon.

In the genesis of neoplasms, as in the genesis of other organic structures, I believe we must take into consideration two factors—the *cells* whence they originate and the *force* that regulates the cellular activities.

With regard to the cells, although each is largely dependent upon others, yet at the same time each manifests a certain independence of autonomy. In the special changes underlying pathological new formations the autonomy of the cells plays an important part. It is quite certain that somatic cells are possessed of far greater developmental powers than they ever ordinarily manifest. Evidence of this is seen in the processes of repair and regeneration, in the changes that take place at puberty, in connection with pregnancy—when the breasts and uterus undergo such remarkable metamorphoses—in the phenomena of compensatory hypertrophy, and in a variety of other processes. Strange to relate, this wonderful reproductive capacity, which enables us to understand how a single cell may originate even the largest neoplasm extant, has received but scant attention from pathologists in explaining the neoplastic process. That the reproductive activity actually manifested by somatic cells usually falls so far short of their potentiality is believed by Spencer to be due to the restraining and modifying influence exerted by the whole organism on their protoplasm, which is thus compelled to the performance of other comparatively subordinate, modified functions. In the performance of these special duties most of the protoplasm is metamorphosed and used up. Hence, in proportion as the cells are highly specialized, their reproductive function is either greatly reduced or altogether lost. But in the higher organisms certain cells never attain a high degree of development; they remain in a lowly organized condition, and serve, according as they are more or less unspecialized, either as germs for reproducing the entire individual or for forming and maintaining the various tissues and organs. Cells of the latter kind abound in all parts growing and capable of growth. They are, I maintain, *the only real cancer and tumor germs.*

In the ordinary course of organic evolution, the processes of cell growth and multiplication go on until the amount of structure proper to the organism has been produced; then they are restricted within certain limits. In the healthy organism this state of balanced equilibrium is maintained throughout the whole life of the individual. Herein we have evidence of a force regulating the growth and development of the tissues and organs in relation to each other, and to the organism as a whole. So long as the growing cells are subject to this normal restraining influence—which has nothing to do with nerves and blood-vessels, themselves integrated structures—they develop in a regular and orderly manner, in accordance with the specific hereditary tendency of the whole. But when, under pathological conditions, this restraining influence is modified or withdrawn, then their potential reproductive activity may become actual. Cells thus emancipated grow and multiply more rapidly than their congeners. This rejuvenescence is the essence of the neoplastic process. Hyperplasia and not inflammation is the starting-point of every neoplasm. Redundant agamic cell generations are thus interpolated in the developmental series, without the concurrence of the conditions necessary for their potentialities attaining a physiological terminus.

The developmental outcome of cells thus abnormally set free depends chiefly upon the degree of emancipation attained. In plants and the lower animals, such cells tend to form new individuals by agamogenesis; but in the higher animals the emancipation is never so complete, and their cells are always more or less differentiated; hence, in these organisms, instead of new individuals, only such structural modifications as neoplasms are produced. Under these circumstances, wherever there is a sufficient supply of nutritive materials, capable of being utilised for growth by the cells of the part, there a neoplasm will arise; that is to say, the abnormally emancipated cells will there grow and multiply more or less independently regardless of the requirements of the adjacent tissues and of the organism as a whole. In other words, a new centre of development has arisen. Thus the process by which cancers and other neoplasms arise may be regarded as a kind of abnormal gemmation, the tumor being the result of the modified superinduced repetition of the developmental process, and its qualities the result of the degree of emancipation of its elements. In the case of malignant tumors, cell potentialities of the highest order have been awakened; hence the *persistence* of the excessive proliferative activity of their constituent cells, which is a notable feature of malignancy.

It follows from the foregoing that the genesis of cancer and other neoplasms is a phenomenon of the same order as discontinuous growth in general.

Traumata, Chronic Inflammation, and Cancer.

Before setting aside views such at the above in favor of the theory of irritants *ab extrâ*, I think strong evidence ought to be forthcoming as to the probability of the latter hypothesis furnishing as satisfactory an explanation of the phenomenon of the disease.

Let us see whether this is the case.

Those who believe that neoplasms are caused by external irritants may be divided into two classes: the Broussaisians pure and simple, such as Virchow, Hutchinson and his followers, who consider that any form of irritation may originate the disease; and the exclusive supporters of the germ theory, such as Soudakevitch, Ruffer, Pfeiffer, and others who maintain that only microbic irritants are effectual.

First of all, let us deal with the former.

I am persuaded that well-ascertained facts justify the belief that repeated irritations of long duration and moderate intensity are, in a certain proportion of cases, the precursors of malignant disease. Further, I am convinced that parts thus chronically irritated may thereby be rendered more apt to take on neoplastic action than they otherwise would have been. In short, there is such a thing as acquired local predisposition to cancer. Thus may we account for the relative frequency with which certain cutaneous cancers are met with in chimney sweeps and other workers in irritant substances, such as tar, paraffin, etc. Here also belong the various "eczema cancers," "lupus cancers," "scar cancers," etc.

Moreover, I believe that congenital blemishes, such as "rests," moles, nævi, so-called "fleshy warts," etc., are likewise more prone to originate malignant disease than corresponding normal structures. That is to say, there is such a thing as congenital local predisposition to the disease. I submit that this is as far as the facts justify us in going.

The Broussaisians, however, are not satisfied to stop here; for from such considerations as the foregoing they draw the unwarrantable conclusion that chronic inflammatory lesions are the *necessary* antecedents of cancer. It is against this doctrine that I protest, and I will now proceed to show its erroneousness.

Those who maintain that cancers are commonly caused by traumata must explain how it is that men, who suffer three times as often from traumata as women, are, nevertheless, only about half as liable to cancers.

Thus of 9,229 consecutive cases of traumata under treatment at four large London hospitals, I have found that 6,856 were males and 2,372 females, or 2.89 males to 1 female. Similarly, of 240,063 deaths from traumata, tabulated by the Registrar-general for the twenty-five years 1848–72, 178,005 were males and 62,058 females, or 2.8 males to 1 female. On the other hand, of 7,878 consecutive cases of cancer under treatment at the above-mentioned hospitals, 2,861 were males and 5,017 females, or 1 male to 1.7 females. Similarly, of the 19,433 cancer deaths in England and Wales during 1890, 7,137 were males and 12,296 females, or 1 male to 1.7 females.

Evidently either these facts must be refuted, or the theory of the traumatic causation of cancer must be given up.

Still more cogent is reasoning of this kind when applied to cancer of the breast; for, whereas men are quite three times as liable to traumata of this part as women, yet they suffer from mammary cancer only in the proportion of 16 to 1,863, or of 1 male to 116 females. Moreover, were mammary cancers thus caused, the *nipple*, *areola*, and *skin* would be more frequently affected than other parts of the breast; but the actual proportion of cancers that arise from the nipple only amounts to 1.31 per cent., while the areola and skin of this region enjoy still more remarkable immunity.

This completely negatives the alleged causation of mammary cancer by pressure of the corset, injury of the nipple in suckling, etc.

Again, the initial lesion of cancer is almost invariably solitary; whereas if the disease were of traumatic origin, it would often be multiple.

As I shall presently have occasion to demonstrate, during the last half century the proportionate cancer mortality has more than quadrupled; but during the same period the liability to traumata has much diminished.

Finally, savages, who are certainly more prone to traumata than civilized beings, are believed to be almost, if not quite, exempt from cancer.

It is a curious circumstance that the advocates of the traumatic theory of cancer causation should have overlooked these obvious facts.

They base their belief in it on statements made by the patients themselves as to the antecedent occurrence of traumata. Of 137 women with mammary cancer interrogated by me, 35 gave a history of antecedent traumata, or 25.5 per cent.; in other words, the most careful investigation directed expressly to this point failed to elicit any previous history of trauma in 74.5 per cent. of all cases. Many of the above affirmations, furthermore, appeared to me to be the outcome of imagination, rather than proving any real causal relationship; and in no case was there evidence that the disease had developed out of induration or other obvious lesions thus induced.

Gross' figures, derived from massing the analyses of various surgeons, are of similar import. Of 1,511 breast-cancer patients, there was history of trauma in 13 per cent., and in one-quarter of these the cancerous tumor seemed to spring from the lump resulting from the injury.

In the cases under my observation it seemed to me that injury was often merely the means of directing the patient's attention to the previously existing disease, of which she had until then been unconscious.

Of one thousand cases of cancer consecutively under my observation there was but a single instance in which the disease immediately followed an injury, and this was a case of so-called acute traumatic malignancy. Yet if traumata were the efficient causes of cancer, such occurrences would be quite common instead of being so infinitely rare.

Moreover, we cannot produce cancer by any kind of traumatism, even in those who are already subject to the disease, and their wounds heal just as do those of the non-cancerous.

The attempts lately made by Gilbert and Roger to produce cancer in the mammæ of old bitches by subjecting them to various forms of mechanical irritation completely failed to attain this end; and Cazin, by rubbing soot into irritated parts, was equally unsuccessful, although the soot was taken up by the cells of the part.

Again, if the traumatic theory of cancer were true, those parts of the body most subject to injuries, such as the upper and lower extremities, the head, face, and neck, would be the commonest seats of the disease, but its actual localization is totally different.

Though a blow, wound, or other injury may sometimes precipitate the formation of a cancer, yet it appears to me, from the foregoing considerations, that such stimuli are of themselves inadequate to cause the disease. I regard the relation of trauma to cancer—to borrow a Darwinian simile—as resembling that of a spark in contact with combustible matter, the result depending upon the nature of the latter rather than upon the spark itself.

Among the more remarkable instances of the influence of trauma in determining the outbreak of cancer reference may be made to the so-called "acute traumatic malignancy," in which, almost immediately after some severe trauma, there is an acute development of the disease at the seat of injury.

I have also seen instances of the acute outbreak of malignant disease after the removal of not very formidable-looking cancers of the breast, uterus, cheek, etc. Such cases are probably due to the dissemination in the wound of particles of the disease, detached during the course of the operation, which become grafted there and grow with renewed energy.

In another class of traumatic malignancy cases it has been observed that the cancerous disease supervenes some time after various operations, such as the removal of non-malignant tumors, especially after ovariotomy for ovarian cystomata.

In his work on "Ovarian Tumors," Spencer Wells gives a table showing the subsequent history of all those who recovered after completed ovariotomy. It was found that 117 had since died, the cause of death being unknown in 29. Of the remaining 88, no fewer than 32 had succumbed to cancer; that is to say, 1 in 2.75. During the same period the cancer mortality in the general population, among women of about the same age, was 1 in 15.

Thus the cancer mortality was nearly five and one-half times greater for those whose ovaries had been extirpated than for those who had undergone no such operation.

Of these 32 cancer cases, in 19 the seat of the disease is not stated, in 3 it was peritoneal, in 3 uterine, in 2 in the pedicle, in 2 rectal, and in the lung, liver, and kidney each in 1 case.

The date after ovariotomy at which death from cancer supervened is stated in 29 cases; 10 died in the first year, 10 in the second, 4 in the third, and 5 at later periods.

In none of the foregoing cases was there any reason to suspect, at the time of ovariotomy, that malignant disease was then present.

In 6 of the 32 operations it is distinctly stated that both ovaries were removed.

Pfannenstiel, who has made a special study of cases of this kind, concludes that the cancerous disease arises from epithelial elements detached from the ovarian cystoma at the time of operation. These, becoming grafted in a new position, take on such luxuriance of growth as eventuates in cancer. I would specially commend the consideration of these remarkable facts to those who are now advocating the removal of the ovaries as a cure for cancer. Such irrational outbreaks of "*furor secandi*" tend to discredit modern surgery.

It is often asserted that cancers of the *breast* are due to antecedent attacks of inflammation or abscess of the affected part, yet no conclusive evidence of this has ever been adduced. Equally destitute of support is the constantly reiterated assertion that the latter lesions are of more frequent occurrence in the cancerous than in the non-cancerous. The following facts are conclusive in this respect:

Winckel has estimated that after 1,000 consecutive *accouchements* mastitis developed in 6 per cent. This, of course, refers only to its frequency after single deliveries in a succession of women, and not to the frequency of its occurrence in regard to the total pregnancies of each woman during her entire puerperal life. To obtain the latter datum, Winckel's percentage must be multiplied by 4.6, this being the average number of *accouchements* of each married woman. Reckoned in this way, it will be found that 27.6 per cent. of all fertile married women have suffered, at some period or other of their puerperal life, from inflammatory disease of the breast. In order to ascertain what proportion of mammary-cancer patients suffer from similar affections I made special inquiries on this subject in 137 cases. Of these, 24, or 17.5 per cent., gave a history of some previous disease of the breast—abscess in 15, sore nipple in 8, and inflammation in 1; and in 6 of these cases the nipples were congenitally malformed.

The above facts prove that cancer patients are less prone to inflammatory diseases of the breast than the non-cancerous. Hence the only basis for this alleged causation is that in a certain proportion of cancer cases inflammatory lesions have preëxisted. Moreover, against the assumed etiological importance of previous inflammatory disease is the fact that in most of the cases the interval between the antecedent disease and the subsequent outbreak of cancer extended over many years, and during this period the breast appeared to be free from any lesion. Of like import is the fact that cancer of the breast is relatively almost as frequent in the single and sterile as in the married, although the former are much less prone to inflammatory affections of the breast than the latter. On *à priori* grounds, no inflammatory lesion seems more likely to be the precursor of cancer than chronic mastitis; and since this disease gives rise to circumscribed induration, its presence can hardly be overlooked. Yet how rarely does mammary cancer ever appear to start in connection with such indurations? I have met with this conjunction only twice in one hundred and thirty-seven cases; hence it seems to me improbable that chronic mastitis plays an important part in the genesis of mammary cancer.

The outcome of all this is, that intrinsic causes are much more important factors in the origination of cancer than extrinsic ones, which are by no means its necessary antecedents. In the vast majority of cases the outbreak of this disease appears to be *entirely spontaneous;* that is to say, it cannot be attributed to the immediate action of any appreciable extrinsic cause whatever.

With regard to *lactation*, Gross' statistics show that of 416 breast-cancer patients, 316, or 76 per cent., had suckled; while 100, or 24 per cent., had not. Of 110 cases tabulated by Velpeau, 60 had suckled, or 54.54 per cent.; and 50, or 45.46 per cent., had not. Winiwarter analysed 102 cases, with the result that 65 had suckled, or 63.8 per cent.; and 37 had not, or 36.2 per cent.

These data afford no proof that suckling predisposes to cancer; and I am at a loss to find any justification for the assertion that the breasts of married women, and of those in whom the gland has been active, are more liable to cancer on this account, than are the breasts of single and sterile women. Mammary cancer is a disease not of the active breast, but of the breast becoming obsolete. Of 71 prolific women with mammary cancer, I have found that in no less than 55 (77.4 per cent.) the disease did not commence until after child-bearing had ceased. Rarely does it arise during pregnancy or lactation. Of 71 prolific women the subjects of breast cancer, interrogated by me, in 3 the onset of the disease coincided with childbirth, and in 2 with miscarriage, and in 4 it occurred during the lactation period. In none of these cases was the subsequent progress of the disease in any way different from the ordinary. In several cases women with cancer already developed subsequently became pregnant, and in due time gave birth to children without any interference with the ordinary course of the disease. It is evident, therefore, that the acute cancers sometimes met with during pregnancy and lactation are highly exceptional.

From the foregoing, as well as from what follows, it will be gathered that the due discharge of natural functions in no way predisposes to cancer.

I have ascertained from carefully gathered statistics relating to the other chief seats of cancer that the evidence as to the association of the disease with preëxisting lesions of the part is of similar negative tenor.

With regard to *uterine* cancer, it is alleged by Emmet and his followers that the disease is almost invariably caused by child-bearing, lacerations, or endometritis or some of the other maladies incidental to the married state; others attach great importance to catamenial derangements, syphilis, and gonorrhœa.

That cancer is a disease of persons whose previous life has been healthy and whose nutritive vigor seems to promise long life, is a statement in which I entirely concur. It accords with this, that the natural functions of cancer patients are almost invariably performed with ease and regularity. The subjoined data show that in uterine-cancer patients the normality of the catamenial function is seldom disturbed. It is noticeable, however, that the flow is established earlier and ceases later in them than in the generality of women, which is an indication of vigorous sexual life.

Of 104 uterine cancer patients interrogated by me, the catamenia had been in all respects normal in 96 and irregular in only 8—scanty 6, profuse 2.

The mean age at which menstruation first began was 14.5 years, and at which it ceased, 46 years.

Just so is it with regard to marriage, for a much greater proportion of uterine-cancer patients have been married than of the female population of corresponding age.

Of 156 women with uterine cancer under my observation, 146 (93.2 per cent.) had been married, and only 10 (6.8 per cent.) were single; whereas in the general population only 79 per cent. of women over twenty-four ever marry.

Of similar import is the great fertility of these cancer patients. Of 143 uterine-cancer cases interrogated by me, only 6 were barren (4.2 per cent.); whereas among women of the general population the amount of sterility has been estimated at 11.6 per cent. The 137 fruitful uterine-cancer patients of my list averaged 5.6 children and 0.9 miscarriages each—the maximum progeny being 13 children and 4 miscarriages (of which there were two instances).

With regard to one-child sterility, there were 10 instances of it, or 1 in 13.7. This ratio is almost identical with that prevailing among fertile married women of the general population.

To sum up, 143 married uterine-cancer patients had between them 767 children and 123 miscarriages, the average being 5.3 children and 0.8 miscarriage each. This amount of fertility exceeds that prevalent in the general community, which averages about 4.6 children per marriage. When allowance has been made for the fact that a considerable proportion of these patients die before the completion of their reproductive life, it will be obvious that their fecundity is even higher than from the foregoing figures it appears to be.

The mean age at first marriage (in 63 of the above cases) was 21.6 years, and the mean age at which child-bearing commenced (in 100 cases) was 21.8 years, both of which averages are considerably earlier than the corresponding figures for married women of the general community. This accords with what I have previously remarked as to the high reproductive energy of these cancer patients.

It will be gathered from what has been stated that uterine cancer is of more frequent occurrence in the married and in those who have borne children than in the single and sterile. Must we infer from this that frequent parturition favors the development of the disease? Certainly no such inference is warranted, for, as the following data show, female cancer patients in general, manifest a similar high degree of fertility.

Thus 15 women with cancer of the rectum averaged 6.3 children and 0.7 miscarriage each; 98 breast-cancer patients averaged 3.4 children and 1.1 miscarriages each; 6 women with ovarian cancer averaged 8.2 children each; 7 patients with rodent ulcer averaged 6.8 children and 2 miscarriages each; and 9 women with cancer of the tongue averaged 4 children and 1 miscarriage each.

From these data it is evident that the high degree of procreative capacity manifested by these women, is merely one of the consequences of that exuberant general health and nutritive vigor which, as I have previously mentioned, is a peculiarity of cancer patients.

It may be inferred from the fact that 10 of the 156 uterine-cancer patients of my list were unmarried, and all save one childless, that virginity is no safeguard against the disease; and if this evidence as to virginity be deemed insufficient, reference may be made to many published cases in which the presence of uterine cancer has been demonstrated in women who presented all the anatomical signs of virginity.

I have ascertained that in the great majority of uterine-cancer cases, the disease does not begin until many years after the final cessation of child-bearing. Of 32 prolific women thus affected, in 28 (87.5 per cent.) the disease did not begin until a year or more after the cessation of child-bearing; the average interval between the cessation of child-bearing and the onset of the disease in these cases was no less than 12.3 years.

Only rarely does cancer of the uterus arise during pregnancy (6 in 97 cases, or 6.2 per cent.), and within a year after parturition its occurrence is equally rare (6 in 97 cases).

These facts corroborate my contention that the outbreak of the disease is independent of the incidents of the reproductive life. In this connection it may be mentioned that the subjects of cancer of the corpus uteri are much less prolific than those with cervical cancer.

Of 31 cases of this kind tabulated by Pichot, Ruge, and Veit, 14 (45 per cent.) were absolutely sterile, and 3 had only 1 miscarriage each, while the remaining 14 had between them 57 children. Thus of these 31 women the average progeny was only 1.8 children each. When we recollect the comparatively late age at which this form of the disease supervenes, the significance of these figures is enhanced.

The ensemble of facts relating to the life history of the subjects of uterine cancer shows that they have almost invariably led regular, sober, and industrious lives. Persons of drunken and dissolute habits are comparatively seldom affected. Of one hundred and sixty uterine-cancer patients consecutively under my observation, not a single one, so far as I could ascertain, had ever been addicted to *prostitution;* and, what is still more remarkable, only one presented undoubted signs of having had *syphilis*.

In this connection the almost complete immunity of uterine-cancer patients from chronic ulcer of the leg is worth noting. Among my cases there was not a single instance of it.

According to Glatter, of 365 Vienna uterine-cancer patients 91 (nearly 25 per cent.) had been prostitutes; but it must be remembered that he arrived at this conclusion in a rather peculiar way—by assuming that all those described in the registers as "Handarbeiterinnen" were, as a matter of course, "Lustdirnen," which seems to be an unwarrantable assumption. At any rate, my experience in this respect is diametrically opposed to Glatter's conclusion, and in this I am in accord with Duchâtelet, Lebert, Walshe, Winckel, Tanner, and Schroeder. The high fecundity of uterine-cancer patients strongly favors my views, for a large proportion of prostitutes are sterile or relatively infertile.

Martin, Bruns, and others think that previous attacks of gonorrhœa predispose to cancer of the uterus; but they have adduced no convincing arguments in support of this theory, which is at variance with all the information at my disposal.

With regard to the influence of *lacerations* in the causation of uterine cancer, some gynæcologists have gone so far as to assert that the disease always or frequently originates in "lacerations." In order to show the fallacy of this view, it is necessary to bear in mind the following facts about lacerations. They are usually confined to the inferior segment of the uterus, and at first labors they are of such frequent occurrence as to be regarded by many gynæcologists as inevitable. Injuries of this kind are almost always multiple, and in the majority of cases the lesion is bilateral, being most marked on the left side, opposite the situation usually occupied by the fœtal occiput. In extent and depth they are variable, but in most cases the injury is only slight. The worst tears are met with after very rapid, or tedious and instrumental labors.

The great frequency of lacerations *per se* is, of course, no reason for regarding them as the cause of cancer, even when the two morbid conditions coexist. In cases of this kind, carefully observed by J. Williams, in not a single instance did the cancerous disease appear to have started from the "laceration."

Against any such theory it may further be objected that if uterine cancer really originated in lacerations it would, like the latter, nearly always be multiple, and its precise seats of origin would correspond with the localities in which "lacerations" usually occur; but in the initial manifestation of the disease none of these conditions is fulfilled.

Moreover, against the assumed etiological importance of lacerations is the fact that the interval between the laceration and the outbreak of cancer extends over many years, and during this long period the uterus appears to be free from disease.

Thus the average age at which child-bearing commenced in my cases was 21.8 years; whereas in the same women the average age at which uterine cancer supervened was 44 years. Thus between the outbreak of the disease and its alleged causation a period of no less than 22.2 years intervened.

Of like significance, as previously mentioned, is the long interval usually found between the cessation of child-bearing and the onset of cancer.

Another indication pointing in the same direction is furnished by the fact that rapid, or tedious and instrumental labors—after which lacerations are commonest and most severe—are relatively rare in uterine-cancer patients. Of 65 cases in my list, in which the character of the labors was noted, in 59 they were natural (tedious or difficult in 9), and only in 6 were they instrumental.

Thus, notwithstanding many allegations to the contrary, no reliable evidence has hitherto been adduced of any connection between antecedent morbid affections of the uterus and cancer. The great majority of the patients under my observation had been remarkably free from previous uterine disease of any kind. Of 137 cases in which special inquiries were made, only 13 had suffered from previous disease of the uterus—*viz.*, leucorrhœa 7, prolapse 3, and endometritis 3. It accords with this that cancer of the procident uterus is comparatively rare.

Thus in the uterus, as in the breast, the outbreak of cancer appears to be entirely spontaneous; and it cannot be attributed to the immediate action of any appreciable extrinsic cause whatever.

The only evidence of any scientific value hitherto adduced in favor of the Broussaisian doctrine of cancer causation is to be found in Volkmann's well-known analysis of 223 cases of primary cutaneous cancer of the extremities. In this connection it must be borne in mind that, although the extremities suffer more from all kinds of traumata, scars, burns, chronic ulcers, etc., than any other parts of the body, they nevertheless seldom give origin to cancer. Of 7,297 consecutive primary cancers analysed by me, only 99, or 1.3 per cent., originated from the extremities; and of these, 72 started from the lower and 27 from the upper.

Now Volkmann found that in no less than 88 per cent. of his cases the cancerous disease had originated in connection with some preexisting lesion of the part; in only 12 per cent. did it appear to have sprung up spontaneously. If the state of things revealed by this analysis could be proved to be really representative of the ordinary mode of development of cancer, these data would be conclusive evidence in favor of the influence of irritation. But I maintain that it is not so. The cases analysed by Volkmann were *not* consecutive cases, but most of them had been recorded at various times by different observers, with the special object of showing the association between cancer and preëxisting local disease, as to the occasional occurrence of which there is no doubt.

The fallacy of accepting these data as typical of what takes place in the ordinary development of cutaneous cancer, is well seen by comparing Volkmann's results with the following analysis of 40 *consecutive* cases of primary cutaneous cancer recorded by myself (Middlesex Hospital Surgical Reports, 1882–89) in which special attention was directed to the question of preëxisting disease of the part. Of these 40 cases, only 11, or 27.5 per cent., were associated with preëxisting lesions—*viz.*, old scars in 4 cases, congenital lesions in 2, suppurating sebaceous cyst, soot wart, wart of eighteen years' duration, recent wound, and chronic sinus, each in 1 case. In other words, the most careful examination, directed expressly to this end, failed to reveal the existence of any preëxisting local disease in 72.5 per cent. of all cases.

By careful inquiries as to the association of the onset of cancer with preëxisting local disease in other parts of the body, I have ascertained that, for these localities also the foregoing conclusions are equally valid.

The Microbe Theory.

Now let us review the position of the microbists. Microbes first began to be heard of in connection with the etiology of cancer in the seventies of the present century; but the possibility of the disease being contagious had been entertained, from time to time, for many centuries past (among others by Tulpius in 1672). Cancer was regarded by Hunter as the product of a morbid poison, which either arose spontaneously or was derived from the contagion of similar diseases, and he compared it with smallpox, syphilis, tubercle, etc. Hunter's views were therefore similar to those of the microbists.

In the modern revival it was among the schizomycetes (bacteria) that specific cancer microbes were first alleged to have been discovered by Rappin, Freire, Scheuerlen, Schill, Francke, Lampiazi-Rubino, Sanarelli, Kubasoff, and others.

Just as this movement was on the wane, attempts began to be made to ascribe the causation of the disease to the presence of parasitic protozoa. More than half a century previously Hake (1839) had noticed that cancer cells often contained certain rounded, hyaline, spore-like bodies, which he regarded as psorospermial parasites. Some years later Virchow also examined these bodies, but he concluded that they were the outcome of endogenous cell-formation and degenerative changes.

The announcement in 1889 that Darier had discovered similar bodies—which he regarded as psorospermial parasites—in connection with "Paget's disease" of the breast, caused the forgotten controversy as to the significance of these bodies, to be reopened. The interest in this question was shortly afterwards greatly increased by the finding of similar bodies in cancer cells from various parts of the body. Thus the question soon became the cynosure of pathological eyes, for the problem of the origin of cancer seemed to concentre in it. Among those who maintained the psorospermial origin of these endocytes were Wickham, Malassez, Metchnikoff, Soudakevitch, Ruffer, Foà, Pfeiffer, and Cattle, while their non-parasitic nature has been just as strenuously upheld by Borrel, Cornil, Gibbes, Ribbert, Pianese, Delépine, Stroebe, Kanthack, and others.

The third great movement in this connection was initiated by Russell, who (in 1890) described certain "fuchsin bodies" as "the characteristic organisms of cancer;" these he regarded as parasitic blastomycetes of the same order as the yeast fungi.

The Italian pathologists Roncali, Maffuci, Corselli, Sanfelice, and others have lately specially insisted upon the importance of the blastomycetes in the etiology of malignant tumors, and similar views are advocated by Braithwaite.

In endeavoring to estimate the validity of the claims of these various microbes to be regarded as the specific cause of cancer, it must be borne in mind that before a disease can properly be called parasitic the parasite must be identified, isolated, and the disease it is alleged to cause must be reproduced by its inoculation. Judged by this standard the microbe of cancer has not yet been discovered, for none of the bodies hitherto described as such comply with these requirements. Of the numerous researches undertaken of late with a view to finding it, all have proved abortive. One after another the alleged discoveries of this recalcitrant organism have ended only in disappointment. With regard to the alleged etiological significance of the protozoa-like bodies found in cancerous tumors, it may be remarked that similar bodies have been met with in many and various non-cancerous diseases (*e.g.*, "glandular endometritis," chronic ulceration, non-malignant neoplasms and cysts, herpes, Darier's disease, molluscum contagiosum, healing wounds, and after artificial irritation); so that, whatever their significance may be, these bodies are evidently not specific cancer microbes. Moreover, in undoubted cases of human psorospermosis, such as those described by Albarran, Eve, and others, the lesions met with bore no resemblance whatever to cancer.

In short, the evidence hitherto adduced as to the existence of a specific cancer microbe is altogether inconclusive. Yet, in spite of this, bacteriologists seem now to be more confident than ever that there must be a specific cancer microbe. I should like to know why, since we can so well account for all the phenomena of the disease without it. It appears to me that the agency of microbes is no more necessary to account for the genesis of cancer than it is to account for the genesis of a tooth or a hair.

Contagion.

Now let us examine the various collateral indications bearing on this subject and endeavor to ascertain their significance. Of the many attempts that have been made to transmit cancer experimentally from human beings to the lower animals—whether by grafting or by inoculation with the juice—the results have almost invariably been negative (Duplay, Cazin, Gratia, Saenger, Senn, Shattock, Klebs, Maas, and others).

Dupuytren fed dogs and other animals for considerable periods with human cancers, but they did not acquire the disease. The dogs that Alibert caused to swallow the discharge from cancerous ulcers, etc., experienced similar immunity.

Recently Boinet, Mayet, and Francke and de Rechter claim to have succeeded in transmitting the disease.

Of Boinet's forty intraperitoneal inoculations of rats with human cancer, one of the animals was seized with paraplegia a month after the operation and died shortly afterwards. On post-mortem examination, it was found to have cancer of the liver and spinal column. Boinet's fifty subcutaneous inoculations gave only negative results.

Mayet, however, claims to have successfully transmitted the disease in a white rat by the subcutaneous injection of a filtered glycerin extract of human cancer. At the post-mortem examination, eleven months after the injection, two pea-sized cancerous nodules were found in the animal's kidneys. Similarly Francke and de Rechter claim to have transmitted human cancer to a white mouse.

It is difficult to determine the validity of such claims, especially when the numerous sources of fallacy are borne in mind. Dogs, rats, and mice in confinement (especially the white varieties) are very prone to develop cancer spontaneously; and in these animals tubercle is a common disease easily mistaken for cancer. Having in view these facts and the great mass of negative evidence, it seems desirable for the present to regard these alleged successes with great reserve.

It is reasonable to suppose that experiments of this kind would have a better chance of success if confined to animals of the same species. The attempts made in this direction by Jeannel, Bert, Senn, Weber, Köster, and many others have, however, all proved abortive.

Hanau (rat to rat), Weber (dog to dog), and Morau (mouse to mouse) now allege that after numerous failures they have at length succeeded; but their results are open to just such fallacies as those above mentioned.

With regard to human beings, there is no proof that cancer has ever been communicated from one individual to another. The attempts made by Alibert, Biett, and others, to inoculate themselves and their pupils with the disease were uniformly unsuccessful. There is not a single case on record of a surgeon having acquired cancer during the performance of an operation for its removal, notwithstanding the frequency of exposure to contagion under such circumstances. Of the thousands of persons habitually engaged in attendance upon the victims of this disease, how few have ever become similarly affected. Notwithstanding that many men have had sexual intercourse with women the subjects of uterine cancer, there is not a single well-authenticated case on record of cancer of the penis acquired in this way. The number of cases in which cancerous disease of the uterus and penis have coexisted in husband and wife is so small as to deprive them of all value as evidence of contagion. I can cite only six cases of this kind, although the frequency of exposure to the risk of contagion is so great, that Noble had no difficulty in collecting the records of one hundred and sixty-six cases of pregnancy complicating uterine cancer, published during the ten years 1886–95. Moreover, it has often happened, that women in whom a previous pregnancy had been complicated by cancer, have again become pregnant; and I even know of instances of pregnancy after supravaginal amputation of the cancerous cervix. Yet of one hundred and thirty-four men with cancer of the penis, tabulated by Demarquay, only one had a wife with uterine cancer. Thus there is every reason to believe that cancer cannot be transmitted from one human being to another.

In this respect, then, the hypothetical cancer microbe fails to make good its entity.

Autoinoculation.

With regard to the autoinoculability of cancer, the evidence forthcoming is so weighty as to be practically conclusive.

In 1888 Hahn successfully transplanted several small cancerous grafts from recurrent disease of one mammary region into the healthy breast of the opposite side. Bergmann and Doyen are reported to have repeated Hahn's experiment, with similar results, thus establishing the autoinoculability of the disease.

I have found very few experiments on record as to the autoinoculability of cancer in the lower animals. Senn's attempts on a dog failed.

In a considerable number of cases it has been observed that when cancerous growths have remained for some time in contact with epithelial-covered surfaces the latter have at length become cancerous, as if by direct implantation.

Cripps has related the case of a woman with extensive cancerous ulceration of the left mammary region, who, being unable to put on any dress, had kept her arm—bent at a right angle—in constant contact with the disease for several months. In consequence of this the skin in the vicinity of the elbow became the seat of a cancerous ulcer several inches in diameter.

A somewhat similar instance had previously been recorded by De Morgan, as follows:

"My colleague, Mr. Shaw, attended a woman whose pendulous breast—the seat at its most dependent part of ulcerated cancer—rubbed against the skin of the thorax. At the point of contact a circular patch of cancerous ulceration (the size of a florin) took place, the intervening skin between this and the fold of the mamma remaining healthy."

Examples of the spread of the disease by "contact infection" from the uterus to the vagina have been reported by Thorn, Czempin, and Fischer.

In one of Thorn's cases, a multipara aged 46—whose uterus had been deflected to the right, where it had become fixed in its faulty position by adhesions—subsequently developed cancerous "cauliflower excrescence" of the portio. Owing to the faulty position of the uterus, the diseased portio was constantly in contact with the left side of the vagina at a considerable distance from the fornix. In this position papillary cancer developed, which fitted the similar growth on the portio "like a saucepan lid." Elsewhere the vagina was free from the disease.

Niebergall, Winter, and Leopold have described cases in which the primary outbreak of the disease in the corpus uteri has been followed by the appearance of similar disease in the cervix, which they ascribe to inoculation by contact with the primary cancerous polyp, or with *débris* given off from it. In like manner, instances have been reported by Hamburger and Walter of the spread of cancer from one vulva to the other.

Facts of similar import have been noticed in various other parts of the body. Klebs has seen instances in which cancer of one part of the alimentary tract has been followed by the development of cancerous nodules of similar structure at other parts lower down, as if by the implantation there of detached fragments. Moxon has described the spread of the disease from the trachea to the lungs in a similar way.

Instances have also been observed of the spread of cancer across large serous cavities, such as the peritoneum. Thus in cancerous affections of the abdominal viscera the pelvic floor has often been found studded with similar cancerous nodules, due to fragments detached from the primary growth having lodged and taken root there. Moreover, cancer of the abdominal viscera, projecting into the peritoneal cavity, is commonly found to have invaded the opposite layer of the serosa, where this comes in contact with it.

Courtin, Reinecke, and others have called attention to the frequency with which, after tapping for ascites due to cancerous disease, the resulting sinus itself becomes cancerous, as if through infection of the wound by cancerous elements contained in the ascitic fluid.

Cases have also been recorded in which the disease had spread by direct implantation from one lip to another (Bergmann), from one vocal cord to the other, from the tongue to the buccal mucous membrane (Lücke), from the visceral to the parietal pleura, etc.

I have myself seen several instances of the kind, especially in the mouth and bladder, in which it appeared to me almost certain that cancerous growths had originated in this way.

There are also reasons for believing that eroded surfaces may become infected through constant contact with the discharge from cancerous ulcers; and many surgeons (Hahn, Donitz, Sabatier, etc.) admit the traumatic dissemination of the disease through infection of wounds by the escape of "cancer juice" during operations.

Schopf reports that, having had to make lateral incisions into the vagina and vulva during the process of vaginal hysterectomy for cancer of the uterus, these incisions subsequently became cancerous, as if from contact infection.

Hence care should be taken to avoid cutting into malignant neoplasms during their removal; for such is the great tenacity of life and the wonderful proliferative power of even the most diminutive fragments of cancer that, when left behind, they only too often constitute fresh centres of disease.

In all the foregoing instances the phenomena met with more closely resemble those of tissue-grafting than they do those resulting from the inoculation of infectious disease. It may be inferred that the morbid epithelial cells are themselves the infecting agents, and that cancer autoinoculability is a phenomenon of the same order as cancer metastasis. The evidence here, as before, is against the existence of a specific cancer microbe.

Hence if there be any irritant *ab extrâ* from whose action cancer must result, it altogether transcends present experience.

Infection.

Lately the attempt has been made to utilise the irregularities invariably met with in the topographical distribution of cancer as evidence of the *infectious* nature of the disease. Arnaudet was the first to formulate these ideas. In certain remote rural districts in Normandy he found that cancer was two or three times more prevalent than in Paris. He also adduced instances of cancers coexisting in various organs of persons living in certain houses or in their vicinity. Hence he concluded that the locality where a cancer patient had lived was contaminated; and he thought it probable that contagion was propagated chiefly through cider, water, etc. Similar instances have since been adduced by Guelliot, Fabre, Fiessinger, and Webb.

According to these views, cancer is an infectious disease, with an incubation period of from a few days to two years, beginning with a primary lesion and being followed by generalisation. Metchnikoff considers that it should be classed with the miasmatic diseases, and that it is probably propagated by spores formed outside the body.

In support of these views it is alleged that the dwellers in certain houses become affected with cancer, either simultaneously or successively, with undue frequency; that instances of the disease attacking two persons (*cancer à deux*) living together are relatively frequent; and that in certain localities so many cases may be met with as to constitute an epidemic.

Webb reports the following remarkable group of cases:

> In a village not far from his residence are two houses under one roof, with water-supply and drainage in common. Let us call them Nos. 1 and 2. Twenty-six years ago a man aged 28, living in No. 1, died of cancer of the rectum. Mr. J. H. and his wife next occupied it. His age then was 60. Two years later he died of cancer of the stomach. His widow, who continued to live in the same house, died in it ten years later of cancer of the rectum.
>
> Prior to her death, Mrs. R., aged 50, who lived in No. 2, was found to have cancer of the breast, which ended fatally eight months later.
>
> After the death of Mrs. J. H., No. 1 was occupied by three maiden ladies. Of these, Miss P. died four years ago, aged 58, of cancer of the uterus; Miss F., who nursed her, died last winter, aged 61, of cancer of the stomach; the other sister is still alive and well.
>
> None of these persons were blood relatives, and in none of the families was there a history of cancer in other relatives.

Fiessinger instances a somewhat similar condition: In a small village a woman died of cancer of the breast, and within a comparatively short space of time two other women lodging in the house died of the same disease—one of the rectum and the other of the vulva; and, after a certain time, two neighbors also died—one of cancer of the stomach and the other of sarcoma of the leg.

On the strength of some exceptional coincidences of this kind, without any other requisite data, the exaggerated conclusion has been drawn that cancer is an epidemic disease, and such groups of cases have been styled cancer epidemics! If the alleged epidemiology of cancer has no surer foundation than this to rest on, the less said about it the better. It will be time enough to entertain such surmises when the cancer microbe has been discovered. What to my mind completely negatives these conclusions is the significant fact that in the crowded cancer wards of the Middlesex Hospital, during the last twenty years, not a single instance is known in which a sister, probationer, nurse, ward-servant, surgeon, student, or any one engaged in attendance on the cancer patients has ever subsequently developed the disease.

Besides, as I shall presently have occasion to show, cancer is of less frequent occurrence in urban than in rural districts, and it is least frequent of all in those parts of the former where the density of population is greatest, and where sanitation is the least regarded. Surely, if the disease were really infectious, it would be in the overcrowded parts of our great towns that we should see the evidence of it, rather than in remote rural districts, whence all the alleged cancer epidemics hitherto reported have hailed from.

The question of the prevalence of cancer in Normandy has lately been investigated by a committee of thirty-five local practitioners, and their conclusion is, that although the disease is unduly prevalent in certain remote hamlets—probably in consequence of heredity—yet, when the whole of Normandy is taken into consideration, cancer is no more prevalent there than in many other parts of rural France. In this connection it should be borne in mind that other diseases besides cancer—deaf-mutism, for instance—manifest topographical variations in their distribution.

The Question of the Origin of Malignant from Non-Malignant Neoplasms.

Important practical issues are involved in the solution of the question as to the alleged liability of non-malignant neoplasms to become malignant. If any such tendency really exists, then these neoplasms ought to be extirpated as soon as possible. Widely divergent opinions have been expressed on this subject. Prior to the application of the microscope to the study of new growths, it was generally believed that every chronic tumor (scirrhus) either was malignant or tended to become so. Thus the old German surgeon Heister, writing in 1731, says: "The name scirrhus is given to a painless tumor that occurs in all parts of the body, but especially in the glands, and is due to stagnation and drying up of the blood in the hardened part." . . . "When a scirrhus is not reabsorbed, or not arrested, or is not removed by time, it either spontaneously or from maltreatment becomes malignant; and then we begin to call it cancer or *carcinoma.*"

The difficulty of then discriminating between malignant and non-malignant tumor-like swellings rendered some such belief inevitable; but, since the establishment of this differentiation, it is surprising to find the old creed still so influential.

We now have to inquire whether, in the light of modern research, this belief is justifiable?

Since innocent neoplasms may inflame, suppurate, ulcerate, necrose, and degenerate, just like physiological parts of the body, it seems not unreasonable to suppose, on *à priori* grounds, that they may also become the seats of malignant disease. The occasional coexistence in the same organ of benign and malignant neoplasms favors this view. Such are the chief considerations which have given rise to the common belief that innocent tumors are peculiarly apt to become malignant.

On critical examination of the subject, two considerations have much impressed me. The first is the rarity with which these two kinds of neoplasms coexist in the same organ; so that, even if we admit that malignant transformation takes place in all such associated neoplasms, the event must be one of great rarity—very much rarer than it would be if non-malignant neoplasms were especially prone to become cancerous.

The second consideration is the inconclusiveness of the evidence as to the malignant growths in most of these cases having sprung from their non-malignant associates. In many instances, it is perfectly evident that the association is a mere coincidence, each neoplasm having originated independently. In other cases, the coexisting neoplasms are more closely associated; but even in these the appearance of the non-malignant neoplasms is often such as hardly to countenance the belief that the malignant disease had sprung from them.

I will now discuss this question more in detail as it affects some of the more important organs.

In the Uterus.—At the outset it must be borne in mind that uterine myomata are of very frequent occurrence. According to Bayle, twenty per cent. of all women over thirty-five are thus affected. If this estimate be correct—and so far as I can judge it is not very wide of the mark—these neoplasms are much commoner even than cancer. Hence, considering the great frequency of both diseases in women of a certain age, we need not be surprised to find them coexisting in the same uterus rather frequently. Thus of 78 uterine-cancer necropsies of my list, in 5 there were concomitant myomata; and of the 45 similar necropsies, tabulated by Lebert, 6 were associated with myomata. Thus in these 123 uterine-cancer necropsies, myomata coexisted in 11, or in 9 per cent.

1. In the immense majority of cases—in four-fifths of those under my own observation—the two neoplasms were quite separate and independent of one another—the myoma having sprung from the corpus

and the cancer from the cervix or portio—so that in these cases there could be no question of the latter disease having originated from the former.

2. In the remaining cases the coexisting neoplasms were much more closely associated, most of them arising in the corpus. A common condition is to find one or more small subperitoneal or intramural myomata, with cancer of the mucosa. Under these circumstances the myoma is seldom cancerous. Of course, when the cancerous disease spreads widely, even tumors such as these may be at length invaded.

A good many instances have been recorded of myomata projecting into the uterine cavity and bearing on their surface a cancerous growth or ulcer. In cases of this kind, the cancerous disease usually spreads from the mucosa to the myoma, by way of the perivascular lymphatics. In like manner uterine myomata, projecting into the abdomen, sometimes become cancerous through extension of the disease from adherent neighboring organs, such as the ovary, intestine, and omentum. There is yet another way in which these tumors may possibly be secondarily invaded by cancer, and that is by dissemination from a primary focus elsewhere, of which Schaper has reported an instance, the primary disease being in the lung.

3. In such cases as the foregoing there is, of course, no question of the cancerous disease having primarily originated in the fibromyoma. Indeed, this is an event of such rarity that, notwithstanding the great activity of modern pathologists, only about a dozen instances of it have hitherto been recorded; and in most of these the evidence adduced is far from being thoroughly convincing. Although Martin, somewhat cavalierly, rejects these cases on this account, there can, I think, be no doubt as to the reality of the occurrence. The following example of it has come under my own observation:

A single woman, aged 43 years, was in a very feeble and emaciated condition. She had suffered from pain and difficulty in defecation for the last twenty-five years. A few months ago an abscess formed in the left ischiorectal region, whence a fistula resulted, and subsequently cancerous ulceration. On examination a crater-like cancerous ulcer occupied the left ischiorectal region. A fistulous tract, discharging fæcal matter, passed from its base into the rectum. There was no vaginal discharge, nor was the portio ulcerated. Left lumbar colotomy was performed, but she died of exhaustion twenty-six days later. At the necropsy the pelvic contents were found matted together. The uterus, distended to the size of a man's fist, completely filled the pelvis. To it the rectum and ileocæcal part of the intestine were adherent. The former was compressed against the sacrum. Immediately above the seat of compression, a fistulous tract passed from the bowel to the ulcer in the ischiorectal region. In the posterior wall of the lower part of the uterus there was a distinctly encapsuled, ovoid new growth, the size and shape of a lemon, presenting the appearance of an intramural fibromyoma, infiltrated with colloid cancer. At its periphery, in a few places, the colloid growth had invaded the adjacent parts, especially the connective tissue between the lower part of the rectum and the enlarged uterus. Opposite the posterior wall of the bladder the capsule of the tumor had given way, and the cancerous disease had fungated into that viscus. Some of the adjacent pelvic lymph glands were infiltrated. The colloid growth presented as a pale, yellowish-white, translucent, coarsely granular substance. In some places it was soft and gelatiniform; in others it partook more of the nature of scirrho-colloid. There were no metastases. Both ureters were dilated, and there was left pyonephrosis with acute nephritis and atrophy.

The disease had the appearance of being much more advanced within the capsule of the fibromyoma than elsewhere. It had invaded neither the mucosa of the rectum nor that of the portio. Hence I conclude that it really originated in the fibromyoma.

Histological examination revealed a scanty, fibrous, alveolar structure, the alveoli containing colloid substance. In many of the sections a layer of columnar epithelial cells, lining the alveoli, could be traced, most of the cells being in an advanced stage of granular degeneration. The presence of these lining cells, together with the occasional appearance here and there of tubules lined by columnar cells, in which degenerative changes had made but little progress, enabled me to recognize the primitive morbid condition as glandular cancer of the tubular type. The section showed in some places tracts of fibromyomatous tissue.

Legnieu and Marien, Coe, Liebmann, Gläser, Klob, and others have also reported instances of cancer originating in uterine fibroids. If such conditions were of frequent occurrence, cancer of the uterus would be more frequently met with in the *corpus* than elsewhere—for it is here that fibroids are commonest—but we know that cancer rarely arises in this situation.

The presence of epithelial structures in uterine fibromyomata, first demonstrated by Babes and Diesterweg, has been confirmed and amplified by many recent observers (Ricker, Orloff, Recklinghausen, Hauser, etc.), who have for the most part identified these structures with residua of the Müllerian and Wolffian ducts. In the normal uterus the deep extremities of the utricular glands often penetrate for some distance into the adjacent musculature and in the so-called "glandular endometritis," this penetration is still more marked. During pregnancy similar changes are very noticeable, and conditions arise which tend to sever the connection of the glands with the free surface. In some such ways fragments of the utricular glands, no doubt, often become sequestrated and embedded in the musculature, of which Hauser and Ribbert have demonstrated instances. The latter observer has even found islets of the mucosa completely sequestrated in the uterine wall. Is glandular tissue from these sources ever included in fibromyomata? Many of the specimens of the above-mentioned observers justify this belief. Such are the sources whence cancerous disease of uterine fibroids probably originates.

It is evident from the foregoing that there is no real incompatibility between uterine fibromyoma and cancer, as Cruveilhier believed. At the same time the extraordinary rarity of this morbid conjunction is certainly noteworthy. In short, it follows from what has been stated that far from uterine fibroids having any special proclivity to become cancerous, they are very much less liable to originate this disease than are the glandular elements of the uterus itself.

Some pathologists have ascribed the association of cancer with uterine fibroids to "irritation," excited by the presence of the latter and the consequent hyperplasia of the mucosa. Thorn has reported an instance of this kind in which the cancerous disease appeared to have been caused by the presence of a large calcified fibroid. If this alleged causation were of common occurrence, we should expect to find fibromyomata more often concomitant with uterine cancer than with any other local variety of cancerous disease. But this is not so, for fibroids coexist with uterine cancer only in 9 per cent. of the necropsies; whereas I have found that they coexist with cancer of other localities to the extent of 18.5 per cent.* It is evident, therefore, that the changes excited in the uterine mucosa, etc., by the presence of fibroids, do not specially predispose to cancer.

According to Chiari, the subjects of uterine fibroids are unduly prone to cancer. Of 25 women with fibroids under his observation, 2 had cancer of the uterus, 1 cancer of the breast, and 6 had cancer of other organs. This is a very slender basis on which to rest such a sweeping statement. If Chiari's view were correct, we should expect to find uterine fibroids much more frequently in the cancerous than in the non-cancerous. But of 159 female cancer necropsies in my list, fibroids were present only in 20, or in 12.5 per cent.; whereas, according to Bayle, fibroids are found in 20 per cent. of all women over thirty-five. Hence Chiari's conclusion must be rejected.

Passing now to the consideration of the alleged proclivity of uterine myomata to become *sarcomatous*, the first fact that strikes me is the great frequency of the former and the great rarity of the latter disease. My analysis of 2,649 consecutive cases of uterine neoplasms shows

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* Of 44 breast-cancer necropsies I found uterine fibroids in 5; and of 37 necropsies for cancer in other localties, fibroids were present in 10 cases.

883 uterine fibromyomata and only 2 sarcomata. In Gurlt's analysis of 4,115 uterine neoplasms the proportion of fibroids to sarcomata is as 481 to 8. Of 205 hysterectomies for fibroids of the corpus, Martin found 4 of the tumors sarcomatous. It is evident from these data that uterine fibroids seldom become sarcomatous; in fact, the metamorphosis is very much rarer than it would be if these tumors really had any special proclivity that way.

Nevertheless, the fact of the occasional origin of sarcomatous disease in uterine myomata has been clearly established by many well-recorded examples. In this connection it must be remembered that fibroids are of composite build, including connective tissue, muscle elements, blood-vessels, and lymphatics, from either of which the sarcomatous metaplasia may arise. The occasional occurrence in these tumors of cartilaginous and even truly osseous structures (Henle, Bidder, Freund, etc.) points to the probability of blastogenic origin; hence corresponding varieties of the disease. Thus, when the morbid process centres in the connective tissue, its elements multiply, destroying the adjacent fibrous tissue, muscle cells, etc. (*myosarcoma, myomyxoma,* etc.); when the blood-vessels and lymphatics are chiefly involved we get telangiectasic (*myosarcoma telangiectaticum*) and lymphangiectasic varieties (*myosarcoma lymphangiectaticum*). In other instances the muscle elements are alleged to be primarily affected and to increase at the expense of the remaining constituents (*myoma sarcomatosum vel myoma levicellulare malignum*). In their recurrences and metastases each of these varieties usually breeds true.

By far the commonest variety of the disease is the *myosarcomatous.* In such neoplasms round- and spindle-celled elements predominate, and there is often a mixture of these. They usually present as polypoid tumors, projecting either into the peritoneal sac or into the uterine cavity, but exceptionally they are embedded in the musculature of the parietes. Their form is nearly always circumscribed, and they are often encapsuled. Their consistence varies with the amount of fibrous tissue present. The following typical example is by Finlay:

A single woman, aged 59 years, had noticed an intra-abdominal tumor in the region of the uterus for fifteen years. It had caused no special trouble until "quite recently," when it rapidly enlarged. She died of acute peritonitis shortly after coming under observation.

At the *necropsy* a smooth, encapsuled, globular tumor, the size of a fœtal head at birth, was found attached to the fundus uteri by a short, narrow pedicle. Its summit was in a state of incipient disintegration. In this vicinity several coils of small intestine were adherent, one of which was perforated by a spur of the neoplasm. The adjacent part of the bladder was similarly affected. The rest of the tumor presented the appearance of a soft fibromyoma. An ordinary subperitoneal "fibroid," the size of a walnut, was attached to the right side of the uterus posteriorly. The cervical mucosa presented several small mucous polypi. Secondary nodules were found in the base of the right lung, in the wall of the left ventricle of the heart, in the left kidney, and in an infraclavicular lymph gland on the left side.

On *histological examination* the uterine tumor was found to be a *myosarcoma*, in which groups of round and spindle-shaped cells were interspersed with fibrous tracts containing unstriped muscle cells. The secondary growths were of similar sarcomatous structure, only the round-celled elements were more abundant.

Ott, Ullmann, Dickinson, Schreher, and many others have recorded cases of this kind.

Examples of *myomyxoma* have been reported by Franqué, Solly, Fenger, Gusserow, etc.

Aslanian, Kahlden, Johannovsky, and others have detailed cases of the telangiectasic variety; while we are indebted to Pick, Keller, Fehling, and Leopold for the description of instances of the lymphangiectasic form.

Examples of *myoma malignum* have been reported by Langerhans, Kahlden, Whitridge Williams, Doran, etc. In this variety of the disease the primary and secondary growths consist largely of spindle-celled structures, which are believed to be identical with the organic muscle cells of ordinary fibromyomata. In short, it is alleged that the structure of these tumors is that of embryonic leiomyomatous tissue. In estimating the value of this distinction, everything depends upon the significance attached to the spindle-celled elements, as to whether these represent young connective or myomatous tissue. In most of the cases of so-called *myoma malignum* hitherto recorded, the evidence adduced as to the myomatous nature of the spindle-celled constituents seems to me to be far from conclusive. No one seems to have applied to the examination of these structures the special technique and reagents requisite for the differentiation of leiomyomatous tissue. The fact that organic muscle cells may multiply by karyokinesis and produce new elements has, however, been demonstrated by Busachi and others.

It follows from what has been stated that the possibility of benign neoplasms taking on malignant characters cannot be denied; but this is a very different thing from admitting that such neoplasms are specially prone to become malignant. This is disproved by the great rarity of the coincidence. Non-malignant uterine neoplasms have no special proclivity to malignant disease; on the contrary, they seem to be less prone to originate such changes than the morphological elements of the uterus itself.

In the Breast.—After the non-malignant mammary neoplasms had been clearly differentiated from the malignant ones by Astley Cooper the partisans of the old belief still maintained that the latter commonly developed from the former. Cooper himself admitted the possibility of such an occurrence. He says: "I believe that if a person has a tumor of the breast which is not malignant, and that it remains so till the change of life takes place, that then an undue action may be excited in the part, and the tumor become scirrhous."

In order to determine the significance attaching to this dictum, in the light of my own experience, I have consulted the records of two hundred and fifty-four consecutive cases of mammary cancer, of which I have preserved a detailed account; and I find that the disease was associated with fibroadenoma in only two instances. In other words, for every case of cancer that had originated under circumstances suggestive of the possibility of its having sprung from a fibroadenoma there were one hundred and twenty-six cases that had evidently originated otherwise. But the relative frequency with which fibroadenomatous and cancerous neoplasms arise in the female breast is, as I have elsewhere shown (*Annals of Surgery*, October, 1891) as 372 to 1,863, or the proportion is 1 to 5. Hence, even if we admit that malignant transformation takes place in all such associated neoplasms, the event must be one of extreme rarity—very much rarer than it would be if fibroadenomatous neoplasms were specially prone to become cancerous.

In many cases of this kind the association is evidently a mere coincidence, each neoplasm having originated from the gland independently, as in the following cases:

In an example recorded by Paget there was found in the breast excised from a woman aged thirty-two a small fibroadenoma that had existed for four years, and far apart from it a hard cancer of four months' duration.

In a case under Bryant's care a scirrhous tumor occupied the lower and axillary part of the right breast, while upon the surface of the gland, between the cancerous tumor and the nipple, there was a quite separate encapsuled fibroadenoma. The patient was a single woman, forty-nine years old.

Richet has recorded an instance of two fibroadenomata of twenty-two years' duration in the lower segment, and cancer of recent growth in the upper segment of the same breast.

Gross, having enucleated three fibroadenomata from the right breast and amputated the left for cancer, found that the latter also contained three fibroadenomata.

Waldeyer met with a cancerous tumor associated in the same breast with eight fibroadenomata.

In other cases, although the coexisting neoplasms are more closely associated, the appearance of the non-malignant tumors hardly countenances the belief that the malignant disease had sprung from them.

The two following cases have come under my observation:

Case I.—A well-nourished, married woman, aged 63, had a small, stationary fibroadenomatous tumor in the upper part of her breast for thirty-five years. During the last two months a hard cancerous growth, the size of a Tangerine orange, had developed in connection with it. She died a few weeks later of syncope from aneurysm of the aortic arch. On examination of the breast after death, it was found to contain a small circumscribed encapsuled fibroadenoma, partially embedded in scirrhous cancer.

Case II.—A large, obese, sterile, married woman, aged 54, thirty-four years ago noticed a tumor in the upper part of her right breast, which slowly increased to the size of a hen's egg and then became stationary. So it remained until three months before I first saw her, when, without injury or other known cause, the tumor began to increase. In this short time it attained the size of the fœtal head at birth. On examination, I found a circumscribed bossy tumor, adherent to the overlying skin, which was reddened in places, but movable over the subjacent structures. Some of the bosses were soft and fluctuating, while others were hard. The nipple was retracted. The axillary glands were slightly enlarged, as well as those below the clavicle. There was no history of cancer in the family. The breast was amputated and the axillary glands were removed. Examination of the tumor after removal showed that the whole of it was distinctly encapsuled. In many parts of the capsule there were extensive calcareous deposits. On section, the bulk of it was seen to consist of large cysts containing brown serous fluid, and there were also numerous small cysts in the adjacent parts; in addition to the fluid many of the cysts contained villous papillary growths. At the sternal side of the main tumor was a solid, yellowish, encapsuled mass the size of a Tangerine orange, which appeared to be of more recent formation than the rest. Microscopical examination of a portion of this revealed duct-like structures, which often contained papillary ingrowths. Examination of the excised axillary glands revealed only inflammatory changes. It was evidently a case of tubular cancer that had developed in connection with a cystic villous papilloma of old standing. Two and one-half months later recurrence was noticed in the mammary region. Seven months later the skin over the whole of the front of the thorax and upper part of the abdomen contained numerous small, hard, cancerous nodules. In the right mammary region these were confluent and ulcerated. The right axilla was infiltrated and the upper limb œdematous. The woman died of right hydrothorax, with collapse of the lung, nearly seventeen months after the operation. At the necropsy the local disease was found to have spread by direct extension through the thoracic wall to the right pleura and lung, both of which contained numerous cancerous nodules. The pleural sac contained seventy ounces of fluid, and the lung was collapsed. There were two caseating tuberculous deposits in the upper lobe of the left lung. The heart was small and fatty. The peritoneum was thickly studded with cancerous nodules. The liver was large and fatty, and the gall-bladder contained three facetted calculi. The spleen and both kidneys were congested. The uterus was small and presented several pedunculated fibroids at its fundus.

Of similar cases observed by others, the following will suffice:

Case I.—A lady, aged 49, under Haward's care, had a firm, lobulated, non-progressive tumor—the size of a bantam's egg—in the upper part of her right breast. After it had remained in this condition for nine years, a hard nodule formed between the tumor and the overlying skin, which presented all the signs of cancer. The axillary glands were unaffected. On histological examination after extirpation, the old tumor proved to be a typical fibroadenoma. In the overlying skin was a button-like nodule of hard cancer, which adhered to the adjacent adenoma, but had only superficially invaded it. Eleven months after this operation two small recurrent nodules appeared in the vicinity of the scar.

Case II.—In an unmarried woman, aged 61, White found a single fibroadenoma in the *left* breast and three similar tumors in the *right* breast. In close association with one of the latter an acinous cancerous growth had sprung up.

Case III.—A woman, aged 44, had noticed from girlhood a stationary tumor, the size of a cherry, beneath the skin of her left breast. Two years before she came under observation hard cancer started in the vicinity of this tumor. When first seen by Hutchinson, Jr., she had a hard cancerous mass there, adherent to the overlying skin. This was excised, and some affected axillary glands were removed. On examination of the part after removal, a rounded fibroadenomatous tumor was found, completely embedded in scirrhous cancer, which surrounded it to the extent of from one to one and one-half inches. On microscopical examination, it was found that the cancerous disease had invaded the structure of the adenoma; but the author is doubtful whether this implies that it really commenced in the tissue of the latter.

Many instances of the development of *sarcoma* in association with mammary fibroadenoma have also been recorded. Labbé and Coÿne believe that most sarcomata of the breast originate thus, rather than from the tissues of the gland itself. In support of this they instance the following case in which an adenocystic sarcoma arose in close connection with an old adenofibroma.

The patient was a woman, aged 44, in whose left breast a hard tumor, the size and shape of a walnut, had existed without alteration for ten years; when, without any known cause, it began to enlarge, and in the course of two years increased to the size of a newly born child's head. It was then removed, together with the breast; and, on microscopical examination, it proved to be a spindle-celled myxadenosarcoma.

Of eight cases of mammary sarcoma examined by these authors, no less than four had a similar history—whence their conclusion. I have not met with such cases in anything like so large a proportion. Among thirty sarcomata of the breast analysed by me, there was only one instance of this kind.

In this case the patient, aged 43, first noticed a small hard lump in her right breast six years before she came under treatment. This lump having remained stationary for over five years, then began to enlarge during pregnancy, and in nine months' time it attained the size of a large orange. On histological examination after removal, it proved to be a solid and spindle-celled adenocystic sarcoma.

Billroth mentions having met with 2 such instances, out of his 19 cases of mammary sarcoma; and of 33 cases collected by Poulsen, in 10 the tumor had existed for over five years—in 4 cases for from five to eight years, in 3 for ten years, in 1 for seventeen years, and in 2 for forty years.

The initial slowness of the growth in such cases is probably due to the paucity of its constituent cellular elements; for, as Virchow has pointed out, young fibrosarcomata are often almost entirely fibromatous in structure; later on their cellular elements increase, and the fibrillar substance becomes less predominant. In some of these chronic tumors, we probably have to do with sarcomatous disease starting from overgrown supernumerary mammary sequestrations. Under these circumstances, I feel bound to reject Labbé and Coÿne's conclusion.

It follows from what has been stated that the possibility of benign mammary neoplasms taking on malignant characters later in life must be admitted; but this is a very different thing from admitting that such neoplasms are specially prone to develop malignant disease. This is disproved by the extreme rarity of the coincidence. Non-malignant mammary neoplasms are, in fact, less liable to originate malignant disease than are the glandular elements of the breast itself.

In other parts of the body where this question has been thoroughly studied similar conclusions have been arrived at.

Thus of 10,747 cases of non-malignant laryngeal neoplasms tabulated by Semon, there were only 47 instances in which malignant disease had supervened.

Multiple Primary Cancers.

It is now generally recognized that cancer may originate primarily from more than a single focus. Pathologists have been aware of this for some time, although it is only recently that the subject has attracted special attention. Such cases are, however, exceedingly rare. The wonder is that they do not occur more frequently, especially if, as alleged, cancer be a parasitic disease.

In the breast, in the uterus, and in most other parts of the body the initial manifestation of cancer is almost invariably solitary. Multiple cancerous foci, in such organs as the breast and uterus, are usually due to lymphatic dissemination; and in some cases probably to autoinoculation or contact infection. According to Gross, two or more nodules are met with as the first obvious manifestation of mammary cancer in about three per cent. of all cases. Leopold, examining cancerous breasts removed at early stages of the disease, when the lesions were quite small, almost invariably found local dissemination. Most of these multiple nodules no doubt arise in this way. In rare instances they may be due to the coexistence of one or more small non-malignant nodules with the cancerous tumor, of which examples have been recorded.

The hyperplastic condition of the glandular epithelia that accompanies the outbreak of mammary and uterine cancer may be regarded as analogous to the ichthyotic changes in the buccal mucous membrane, that so often coexist with cancer of the tongue, mouth, etc. In connection with these ichthyotic areas of the buccal region, independent outbreaks of cancer have often been observed; and it is highly probable that hyperplastic glandular elements in the breast and uterus occasionally originate multiple cancerous growths in like manner. Similar conditions may be met with in all parts of the body where cancer arises. They are the first indication of altered epithelial activity, of which, in a more advanced stage, cancer is the outcome.

Nearly allied to these independent outbreaks are those cases in which, after operation, with freedom from recurrence for long periods, the disease at length returns in the vicinity of the primary lesion; a fresh outbreak arising, as Heidenhain believes, from proliferating glandular elements, left behind at the primary operation.

In no part of the body does the initial outbreak of cancer so frequently manifest itself in the form of multiple foci as in the *skin*—especially the skin of the face. In these cases hyperplastic changes of the adjacent integument almost invariably coexist. The persons thus affected usually are workers in tar, paraffin, etc., as in the following case:

An asphalter, aged 72, came under treatment with three widely separated cancerous lesions on different parts of his face: 1. The largest presented as a rounded epitheliomatous ulcer, about two inches in diameter, at the outer angle of the left orbit. Histologically the lesion consisted of anastomosing branching ingrowths of the deeper parts of the epidermis into the subjacent tissues, but no "nests" were to be seen. It was of six months' duration, and a "pimple" had previously existed at the starting-point of the disease.

2. A second much smaller cancerous lesion was met with in the right temporal region, just above the zygoma. It was of two months' growth. Microscopical examination revealed in the dermis rounded groups of closely aggregated wavy epithelial tubules, full of cylindrical epithelial cells. It had evidently sprung from the sweat glands; the epidermis, sebaceous glands, and hair follicles were unaffected.

3. The third cancer consisted of a small scab-covered warty excrescence, which occupied the middle of the right cheek, and was of one month's duration. It consisted, like the first, of ingrowing interpapillary epithelial processes, and the sebaceous glands were greatly hypertrophied. The peripheral cells of the ingrowths were palisaded, the central ones flattened and cornifying; but there were no "nests."

The integument adjacent to each ulcer was in a state of chronic seborrhœa, and the skin of the nose and ears was similarly affected. The adjacent lymph glands were not enlarged. The backs of both hands were covered with warty outgrowths and thickened epidermis, which the patient ascribed to irritation of sulphur used in his work as an asphalter.

Thus of these three primary cancerous growths two had originated from the deep part of the epidermis, and one from the sweat glands. In each case the seborrhœic outbreak preceded the outbreak of the cancerous disease, and was by no means limited to the precise starting-point of the latter.

Similar cases have been reported by Volkmann, Tillmanns, Schimmelbusch, and others. In chimneysweeps I have seen the scrotal integument similarly affected. Tillmanns has met with an instance of epithelioma of the integument of the forearm and of the scrotum, in a paraffin worker. In old persons multiple cutaneous cancers sometimes arise in connection with chronic seborrhœa. Primary multiplicity is also often seen in cases of rodent ulcer, especially in aged subjects. It will be noticed that in most of the cases just mentioned the outbreak of the disease appears to have been determined by some form of local irritation; which, it may be surmised, acted as fuel to the fire of preëxisting epithelial proliferation.

A very rare form of initial outbreak is the simultaneous appearance of the disease in both of paired organs, such as the breasts; 2

instances of this occurred in the 1,664 cases of mammary cancer collected by Gross. Billroth, Aitken, Klotz, Volkmann, and others have met with cases of this kind.

A similar state of things is occasionally observed in other paired organs, such as the testes, ovaries, kidneys, etc. Mandry has recorded an instance of symmetrical cancer of both legs, and another of both ears. Another instance of symmetrical cancer of the auricles has lately been reported by Sampter. Of 263 cases of primary cancer of the extremities, analysed by Michael, 2 were symmetrical. In most of these cases there was preëxisting disease of the affected parts, such as eczema.

It is by no means rare to see cancer of one breast followed, after a time, by outbreak of the disease in the other. The great majority of these cases are, however, due to direct extension of the primary disease, or to its dissemination. Yet it occasionally springs up independently in the opposite breast, as in the following case:

An unmarried woman, aged 60, twenty-one months before I saw her first noticed a hard lump, the size of a Brazil nut, in the middle of her left breast; four months later a similar lump was discovered in the middle of her right breast. When she came under my observation the central part of each breast was occupied by a large hard tumor, to which the overlying purplish skin was adherent, both nipples were retracted, and the glands in both axillæ were enlarged. Her face had a peculiar pinched expression, and she was very emaciated, but not sallow. She died of asthenia ninety-nine days later, without having undergone any operative treatment. At the necropsy the cancerous growths in each breast were found to have increased somewhat in size, but neither had ulcerated. Both were extensively adherent to the overlying skin and to the subjacent structures. The glands in both axillæ were cancerous, and the liver contained a cancerous nodule the size of a pea and four small angiomatous growths.

The three subjoined cases evidently belong also to the same category.

Case I.—A patient seen by Bucher, remained free from any return of the disease for six years, after amputation of one breast for cancer, and then the disease sprang up in the other breast.

Case II.—A woman, aged 48, under Bryant's care with cancer of the right breast, without obvious disease of the axillary glands. Ten years previously her left breast had been amputated for similar disease. The right breast was now amputated. Three years later, when last heard of, the patient was well and free from any return of the disease.

Case III.—The patient, aged 60, when first seen, had scirrhous cancer of her right breast, of eight months' duration, there being no disease of the axillary glands. Two years and a half previously, her left breast had been amputated for ulcerated cancer of several years' duration, but which had not affected the axillary glands. The right breast was now amputated, without opening the axilla. She soon recovered, and was free from recurrence when last heard of, eighteen months later.

Eders reports two cases in which, after extirpation of the breast for cancer, without local recurrence, the disease reappeared in the opposite breast four and seven years respectively after extirpation of the primary disease.

Nunn has recorded an instance of tubular cancer (with cysts) of the left breats, coexistent with atrophic acinous cancer of the right breast.

The patient was a lady, aged 57, in whose left breast—near the nipple—a small tumor was first noticed six years previously. This gradually increased to a large size, and was associated with occasional sanious discharge from the nipple. There was no enlargement of the axillary glands. The affected breast was amputated. The tumor consisted chiefly of one large thin-walled cyst, with a few nodules the size of hempseed projecting into the cavity. These, on microscopical examination, presented the appearance of tubular cancer. She remained well after the operation for three years, when her health began to fail, without any obvious cause. In the course of medical examination of the chest, atrophic acinous cancer of the right breast —which she had hitherto carefully concealed—was accidentally discovered. She died of this disease a few months later. There was no necropsy.

The following somewhat similar case by Mandry is of interest.

A multipara, aged 43, had in the right breast a cancerous tumor the size of an apple, of four months' duration. It was adherent to the pectoral muscle, and the axillary glands were enlarged. The breast was extirpated, together with the pectoral muscle and the axillary glands. Histologically the tumor proved to be ordinary acinous (scirrhous) cancer. Three months and a half later, recurrence was first noticed in the old cicatrix. A fortnight previously a nodule had been noticed in the left breast. The latter soon increased, and the glands in the left axilla enlarged. The local recurrence was then excised, the left breast was extirpated, and the left axilla was cleared. On histological examination of the tumor in the left breast, it proved to be tubular cancer.

In a case of Küster's (reported by Michelsohn) the right breast of a woman, aged 43, was extirpated for acinous cancer of one year's duration; five years later there was recurrence in the scar, with the formation of a tumor in the left breast, which microscopical examination after removal proved to be tubular cancer.

In the *uterus* a few instances of true primary multiplicity have also been demonstrated. Hofmeier and Winter have collected several such cases, in which squamous-celled cancer of the portio was associated with cylinder-celled cancer of the glands of the corpus or cervix. Schauta and Binswanger have added to this list; and J. Williams has met with an instance in which two cylinder-celled glandular cancers of the canalis cervicalis—one near the os internum and the other near the os externum—were found associated with squamous-celled cancer of the portio.

Multiple cancers situated in different parts of the body can be regarded as primary only when each has developed from the epithelium of its own locality, and consequently when each has usually different histological structure.

The following cases illustrate the independent outbreak of the disease in the *breast* and *uterus*.

Broca has recorded an instance in which, after mammary cancer had existed for two and a half years, the cervix uteri became cancerous. Six months later no sign of cancer had appeared elsewhere. The uterine disease here presented every indication of being of independent origin.

Mercanton reports the three following examples:

Case I.—A woman, aged 48, had hard cancer of the right breast and secondary disease of the axillary glands. The diseased breast was extirpated, and the axilla cleared. Nine weeks later cancer of the cervix uteri was discovered and excised. About eight months after the mammary extirpation the disease had recurred *in sitû* and in the axilla; it was again removed from these situations. Six months later she came under treatment again, with further recurrence in the right mammary region and in the left breast. These were removed by operation, and a month later secondarily diseased glands were removed from the left axilla. About this time there was noticed free discharge from the vagina; on examination the uterus was found to be fixed and the cervix infiltrated with hard cancerous growth. Six months after the last mammary operation there was extensive recurrence in both pectoral regions and in both axillæ.

Case II.—In a patient, 48 years of age, there was a hard cancerous tumor in the left breast of two years' growth. It was adherent to the overlying skin, and the axillary glands were invaded. The portio vaginalis uteri was replaced by a large, fungating, hemorrhagic, cancerous outgrowth.

Case III.—A woman, aged 51, in 1889, began to suffer pain in defecation. In the summer of 1890 induration in the left breast was noticed. In November of the same year she was found, on examination, to have cancer of the breast and cancer of the corpus uteri.

Russell, of Baltimore, met with two instances in which, after vaginal hysterectomy for cancer, without local recurrence, cancer of the breast subsequently developed independently.

Zeiss has reported an example of the independent outbreak of cancer in the vulva, breast, and uterus.

The patient was a robust-looking woman, aged 38, the mother of three children. There was an eroded cancerous tumor, of five months' duration, in the right labium minus. The adjacent lymph glands were not obviously affected. The diseased part was amputated with Paquelin's cautery knife. Two years later she became pregnant, and at term was safely delivered of a healthy child. When suckling, she noticed a lump in her left breast, which gradually increased. Two years later irregular metrorrhagia set in. Five years after extirpation of the labial cancer, Zeiss again examined her. The portio and cervix uteri were destroyed by cancerous ulceration, the scar of the old operation remaining healthy. The left breast was the seat of a hard cancer, with enlargement of the axillary glands. The woman was much emaciated, but there was no evidence of other organs being affected.

As instances of associated *mammary* and *ovarian* cancer, in which each neoplasm probably originated independently, the following cases are interesting.

Case I.—The patient, aged 53, the mother of two children, came under Poupinel's observation on account of a left ovarian tumor, with symptoms of one year's duration. During this period she had been tapped nine times. A multilocular cystic cancer of the left ovary was removed by laparotomy. She made a good recovery. About nine months later she again came under treatment, with a cancerous neoplasm of a year's growth in her left breast, and enlarged axillary glands. For twenty-one years she had been aware of the existence in the diseased breast of a hard, indolent, stationary tumor, the size of a hazelnut; and the present tumor seemed to have started in connection with this. The breast was extirpated, and the axillary glands were removed. Recurrence in the mammary region soon afterwards set in, and the growth was extirpated. Seven months later there were further recurrences in the pectoral region, and ascites developed, with nodular masses in the abdomen. Finally, double pleural effusion supervened, of which she died. There was no necropsy.

Case II.—In Mercanton's case the patient was an unmarried peasant, aged 47, who had suffered from uterine prolapse for four years. Not the least interesting feature in her case is the extraordinary series of operations she underwent in the course of a few years; which must, I should think, be unique even in continental experience, where the *furor secandi* is at its highest. For the prolapse the following operations were done: anterior colporrhaphy with perineoplasty, Alexander's operation, excision of the portio, and extirpation of the vaginal mucous membrane. Prolapse of the anus having supervened twelve months after the first of these operations, the actual cautery was applied to the rectoanal region. While this lesion was healing, fourteen months after admission, a hard nodule, the size of a nut, was noticed in the left breast, with enlarged axillary glands. For this the breast was extirpated and the axilla cleared, sixteen months after her admission into hospital. On histological examination the tumor proved to be acinous cancer. The uterine prolapse having returned, a further operation—hysteropexy—was done for it. She soon recovered, and left the hospital in good health a month later. She returned three months afterwards with a left ovarian tumor. For this laparotomy was done, and both ovaries being found affected with soft cystic cancer, they were removed. A few months afterwards she left the hospital convalescent. Two and a half years later she again came under treatment, with an intraabdominal tumor of the left sacroiliac region. Laparotomy was again performed, when the sigmoid and rectum were found embedded in a hard mass of cancerous growth, and the peritoneum was infiltrated. Under these circumstances an artificial anus was established at the abdominal wound. From the operation this poor peasant woman again recovered, but subsequently she succumbed to the disease.

Several instances of *uterine* and *ovarian* cancer, independently arising, have been reported by Reichel and others.

In a woman, aged fifty-three, Mercanton found the disease affecting the *uterus* and *vulva.*

In the following case, under my observation, a patient who had suffered for many years from *rodent ulcer of the face* at length developed *mammary cancer.*

She was a widow, aged 77, who, nine years previously, first noticed a small rodent ulcer at the inner angle of the left orbit. The disease progressed but slowly. After it had lasted for seven years, hard cancer developed in the left breast. The latter disease progressed rapidly, and she died from it rather more than two years after its first appearance. No operation was ever done for either cancer. At the necropsy the left mammary region was occupied by an adherent mass of hard, ulcerated cancer, and the adjacent soft parts were extensively infiltrated. The axillary glands were invaded, and there were several cancerous nodules in the skin of the left arm. The rodent ulcer was still of no great size. The left lung was collapsed, and its apex was bound to the chest wall by old adhesions. There was about a pint of blood-stained watery fluid in the pleural cavity. The right lung was emphysematous. The liver was atrophied, and the gall-bladder full of calculi. The right kidney was also atrophied, and its pelvis contained a large calculus. Several fibromyomatous tumors were connected with the uterus; one, the size of a duck's egg, was calcified.

Hutchinson says he has several times seen similar coincidences. In one of his cases the patient, who had suffered long from Paget's disease of the nipple and *cancer of the breast,* had also a *rodent ulcer of the left eyebrow.*

The three following somewhat similar cases were observed by Bryant:

Case I.—A widow, aged 74, had atrophic cancer of the *right breast* of twenty-six years' duration, that had been ulcerated for thirteen years. Epithelioma of the *nose* then supervened, the breast cancer having remained nearly stationary for many years.

Case II.—A childless, married woman, aged 63, had an epithelial cancer of her *nose* excised. Five years later she came under observation again, with hard cancer of her right *breast* of eight months' duration, of which she died two years later. There was no return of the nasal cancer.

Case III.—A thin, feeble woman, aged 60, with an ulcerated scirrhous cancer of the central part of the left *breast* of eight or nine years' duration. During the last five years there had been increasing difficulty in swallowing, and for some months she had been able to take only fluids. Stricture of the *œsophagus* was discovered—passable only by the smallest bougie—which had every appearance of being cancerous.

Poulsen mentions the case of a woman who died of cancer of the *stomach* five years after extirpation of the *breast* for cancer, of which there was no recurrence.

A similar case has lately been recorded by Gibson: A woman, aged eighty-two, whose right breast had been amputated for cancer twenty years previously, without recurrence, died of cancer of the pylorus.

Dobson had a patient with a primary cancer of the *breast*, who remained well and free from any return of the disease for six years after its amputation, when epithelial cancer of the *tongue* supervened, of which she soon died.

In a woman rather over sixty, Michelsohn met with hard cancer of the right *breast* and cutaneous epithelioma of *the right ala nasi.*

Panas mentions having seen a case of cancer of the *breast in a man*, aged sixty-five, from whom Velpeau had excised an epithelioma of the lip, fifteen years previously; and Graviller has met with a case of cancer of the *male breast* associated with epithelial cancer of the *lip.*

As examples of the association of *uterine* cancer with the independent existence of the disease in other parts of the body, the following cases will suffice:

Bard has seen squamous epithelioma of the *uterus*, associated in the same person with cylinder-celled cancer of the head of the *pancreas ;* Beck found the same variety of uterine cancer coexisting with cylinder-celled cancer of the *sigmoid* flexure of the colon; and Walshe mentions an instance of the association of cancer of the *stomach* and uterus.

Primitively multiple cancerous growths have been met with in a variety of situations other than those associated with mammary and uterine cancer, as in the following cases:

A man, aged fifty-two, came under my notice with *rodent ulcer of the face;* who, fifteen years previously, had undergone excision of *epithelioma of the lower lip,* of which there was no return.

In a man, aged seventy-four, Beck met with cancer of the pyloric part of the *stomach,* developed from the mucous glands, and with colloid cancer of the *cæcum,* developed from Lieberkühn's follicles.

Abesser has reported an instance of squamous epithelioma of the *tongue,* with colloid, cylinder-celled cancer of the *jejunum.*

Kaufmann excised a squamous epithelioma of the *upper eyelid,* from a man who died six months later of cylinder-celled cancer of the *rectum.*

Squamous epithelioma of the *vulva* and cylinder-celled cancer of the *colon* coexisted in Chiari's patient; and cancer of *bladder* and *stomach* in Szumann's.

Schimmelbusch mentions having met with a case in which squamous epithelioma of the *ear* was associated with similar disease of the *lower lip;* and a man was under Billroth's care with cancer of the *stomach,* whose *ear* had previously been excised for epithelial cancer.

Hutchinson has found cancer of the *pylorus* coexisting with squamous epithelioma of the *skin of the abdomen.*

Instances of the coexistence of *ovarian* and *gastric* cancer, and of *ovarian* and *intestinal* cancer, have been recorded by Lubarsch, Krönlein, and others.

Association of Cancer with Other Neoplasms.

As examples of the coexistence of *mammary cancer* with *sarcoma,* I can cite the following cases:

Case I.—A married woman, aged 55, the mother of seven children, six years ago first noticed a small lump on the *left* breast, which made little progress until four months ago, since then it has rapidly increased. When she came under treatment this breast was occupied by a mobile, elastic, nodular tumor, eleven by ten inches; but there was no enlargement of the axillary glands. At the same time the *right* breast was the seat of a typical scirrhous *cancer* of one and a half years' growth, the nipple being retracted and the axillary glands enlarged. The left breast was amputated, and the patient made a good recovery without recurrence; but she died two and a half years later from the cancerous affection of the right breast. On histological examination the excised mammary tumor proved to be a small round and spindle-celled *adenosarcoma.*

Case II.—Billroth has reported a remarkable instance of *cystic* *sarcoma* of the left breast—locally recurrent after amputation, the axillary glands being unaffected—in which, a little later, *cancer* of the right breast supervened, with secondary affection of the axillary glands, and death from internal dissemination.

CASE III.—Some time ago a case was brought before the London Clinical Society by Kesteven, in which, six years after extirpation of *recurrent mammary cancer*, without any local return of the disease, the patient developed *cancer of the rectum* and *sarcoma of the femur*, of which she subsequently died.

CASE IV.—A healthy-looking woman, aged 64, consulted Bryant for a smooth, ovoid, elastic tumor, the size of a cocoanut, which occupied the right mammary region. It was of eight months' growth. In the left breast was an *atrophic scirrhus*, which had existed for sixteen years. Over the left hip was a *fatty tumor*, the size of the fist, of twenty-five years' duration. The right breast was amputated, and upon examination after removal the growth proved to be a mixed-celled *sarcoma*, in which spindle cells predominated. Recurrence at the primary seat soon set in, and after another operation there was likewise speedy recurrence, and so on for the next four and a half years, during which time sixteen operations were performed. When last heard of she was then still in good health, and the cancer of the left breast continued unprogressive.

CASE V.—Multipara, aged 50, whose left breast was amputated by the same surgeon for *cancer* of two years' duration, four years later had *melanotic sarcoma* develop in a mole of the skin of the left axilla. In the course of six months this increased to the size of a hazelnut, when it was excised and never returned. There was no recurrence of the original cancerous disease until more than eight years after the operation, when it reappeared in the mammary region and elsewhere, and caused the patient's death some months later.

CASE VI.—In another case, also under the same surgeon, a single woman, aged 40, had an ulcerating *melanotic sarcoma*, the size of an orange, in the right axilla. It originated there, in a cutaneous mole, two years previously. The patient remained well for nearly four years after its excision, when the breast of the same side began to enlarge. Six months later a *cancerous growth* was found there. The scar of the old operation was sound and free from recurrence. The breast was amputated; and eight years later the patient was in good health and free from any return of either disease.

CASE VII.—Two years after amputation of the breast for primary *cancer*—of which there was no return—a patient of Dobson's developed small round-celled *sarcoma* of the tonsil.

Guende has seen *sarcoma of the choroid* develop in a woman the subject of *mammary cancer*.

Niebergall has published an instance of *cancer*, *sarcoma*, *fibromyomata*, and *mucous polypi* coexisting in the same uterus.

Examples of the association of *cancer* and *sarcoma* in the same uterus have been met with by Emanuel, Rabl-Rückardt, Keller, and others.

A few instances of *mixed malignant neoplasms*—forms in which sarcomatous and carcinomatous processes go on simultaneously—have been reported; as an example of this in the breast reference may be made to Heurtaux's case of *acinous cancer* with *ossifying and chondrifying sarcoma*, the history of which I have previously detailed. In this case the mixed nature of the disease was proved by the nature of the secondary growths, which reproduced all the peculiarities of the primary tumor.

Instances of mixed malignant tumors in the uterus have been reported by Maier, Kuhnart, Rosenstein, and others. Most cases of this kind would now probably be classed as malignant endotheliomata.

Hutchinson mentions the case of a woman who died of *cancer of the uterus* ten years after the extirpation of an eye for *melanotic sarcoma*, of which there was no return.

As examples of the coexistence of cancer and sarcoma in the same person, elsewhere than in the breast and uterus, I can cite the following cases:

Backer has reported the history of a man, aged 52, with *rodent ulcer* of the left ala nasi of nineteen years' duration, who had also rodent ulcer of the right ear of thirteen years' duration, and rodent ulcer of the right upper eyelid of one and one-quarter years' duration. In addition to these lesions he had also an eroded, *melanosarcomatous growth* of the right cheek, the size of a crown piece, which he had noticed for seven or eight years. He had also a pigmented hairy wart on the right side of his forehead, together with comedones, acne, and chronic seborrhœa of the face.

Ricord instances cases in which both *sarcoma* and *cancer* simultaneously coexisted in the nares with mucous polypi.

Langton reports the case of a man, aged 46, with *rodent ulcer* of twelve years' duration, just below the lower eyelid, which was first excised two years after its appearance, but recurred six years later, when it was again removed. Two years later it reappeared for the third time, and again recurred a few months after removal. About this time signs of a growth within the antrum became obvious. The superior maxilla was excised, together with the overlying skin and the rodent ulcer. The patient left the hospital free from any return of the disease, after rapid convalescence. The growth within the antrum proved to be *sarcomatous*.

Cutler has met with *sarcoma of the ovary* coexisting with *cancer of various thoracic and abdominal organs*.

In a woman, aged 52, dead of purulent peritonitis after extirpation of the uterus by laparotomy for myoma, Lubarsch met with sarcoma of the bladder, a large polypus of the stomach, a small tumor of the spleen, "struma suprarenalis aberrans," "lipoma" of the right kidney, cystic kidneys, and enchondroma of the right pleura.

Whitridge Williams has reported an instance in which a *myoma* of the uterine wall was secondarily invaded by *sarcoma* of the overlying mucosa.

It not uncommonly happens that uterine *cancer* is associated with various *non-malignant uterine neoplastic manifestations*, of which fibromyomata and mucous polypi are the commonest.

Of 79 uterine-cancer necropsies, fibromyomata were met with in 5, or in 6.3 per cent. In most of these cases mucous polypi, in the vicinity of the os uteri externum, were also present, and in several other cases as well.

Cancer of the uterus is occasionally complicated by *ovarian cystoma*, but of my 79 uterine-cancer necropsies, there was not a single example of it. Lebert, however, reports having met with 3 cases of ovarian cystoma in his 45 uterine-cancer necropsies.

Hulke found a large *dermoid cyst* filled with hair, surrounded by several smaller cysts connected with the uterine appendages, in the body of a woman who had died of uterine cancer; several similar congenital cysts were attached to the under surface of the liver.

De Morgan and Murchison have both seen uterine cancer associated with *multiple lipomata* of various parts of the body.

Of various non-malignant tumors—not affecting the breast—met with in patients having mammary cancer, I have found *uterine fibromyomata* and soft polypi by far the commonest. Of 44 consecutive necropsies, the former were present in 5 (11.3 per cent.), and in 3 of these cases there were soft polypi as well. Of 123 similar necropsies, tabulated by Nunn, uterine fibromyomata were present in 20.3 per cent.

Next in frequency come *ovarian cystomata*, of which there were 3 examples in my 44 necropsies, 1 each as follows—dermoid, parovarian, and ovarian.

A single woman, aged 56, came under my observation with scirrhous cancer of the right breast and a few enlarged axillary glands. In the left iliac region there was also an ovarian tumor, the size of a man's fist. The breast was amputated and the axilla cleared. She was soon convalescent. Shortly afterwards a multilocular cystoma of the left ovary was removed by laparotomy. There was no sign of malignant disease in connection with it.

Of 86 consecutive cases of mammary cancer, I found *fatty tumors* present in 2. One of these patients had a subcutaneous lipoma over the right deltoid muscle, and at the upper and outer part of the right thigh a pendulous *molluscum fibrosum*, the size of a bantam's egg, and several smaller ones at the back of the neck. After death she was found to have also a *dermoid cyst of the left ovary* and a *soft polypus of the cervix uteri.*

ETIOLOGY.

THE INFLUENCE OF SEX.

The influence of sex in determining the localisation and qualities of neoplasms is very great; and this is specially true of cancerous neoplasms. Not being aware of any comprehensive statistics on this subject, embracing a sufficiently large number of cases to be thoroughly reliable, I have made an analysis of 14,480 primary neoplasms of all kinds, under treatment at four large metropolitan hospitals during the sixteen to twenty years preceding 1888 (*Annals of Surgery*, October, 1891). This list comprises 7,878 consecutive cases of cancer —2,861 males and 5,017 females, or the proportion is 1 male to 1.7 females.

The mortality returns of the registrar-general for the twenty-five years 1872–48, which include all kinds of malignant disease, give a proportion of 1 male to 2.29 females; 1 male died of cancer to every 100 male deaths from all causes, and 1 female died of this disease to every 41 female deaths.*

Analysis of the registrar-general's returns for 1889 shows that 1 of every 21 males and 1 of every 12 females, who reached the age of thirty-five, eventually died of cancer.

I have discovered a remarkable feature with regard to the relative sex liability to cancer, *viz.*, that the difference in this respect has been steadily diminishing ever since 1850. Thus, while the sex ratio for the decennium 1851–60 was 1 male to 2.2 females; for the decennium 1861–70 it was 1 to 2.1; for the decennium 1871–80, 1 to 1.9; for 1881–90, 1 to 1.7; for 1891–95, 1 to 1.5; and for 1896, 1 to 1.4.

As I shall presently have occasion to mention, this alteration in the relative sex liability is due to the increasing cancer mortality having fallen unduly on males. Thus, while from 1851 to 1890, the increase for males was 169 per cent., for females it amounted only to 91 per cent.

In 1894 the cancer mortality of England and Wales was 555 per

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* During this period the total mortality amounted to 10,512,146—of these 5,419,865 were males and 5,082,281 females. The total cancer mortality was 177,300; males 53,867, females 123,433. Thus the cancer mortality averaged 1 in 59 of all deaths.

1,000,000 living for males; whereas for females it was 861. During the same year 1 male died of cancer for every 31 male deaths from all causes, and 1 female died of this disease for every 18 female deaths. Thus, in England, the female liability to cancer now is considerably less than twice that of males.

In the United States and in Europe a very similar sex ratio prevails. Thus, according to the tenth United States census report (1880), the cancer mortality per 1,000,000 living was 205 for males and 354 for females; of 100 male deaths, 1.30 were due to cancer, and of 100 female deaths, 2.35.

The greater prevalence of the disease among women is entirely due to the frequency with which, in them, the mammæ and uterus are affected, the corresponding structures in males very rarely originating the disease; while in all other localities the male liability preponderates.

I know of only two countries in the whole world, where cancer is more prevalent among males than among females; and these are New South Wales and New Zealand. According to Mullins, the cancer mortality of New South Wales per 1,000,000 living—for the period 1890-93—was 416 for males and only 405 for females; and this excess of male mortality has been constant ever since 1870. Of 1,907 deaths from cancer, 1,045 were males and 862 females.

With regard to New Zealand, Macdonald points out that cancer is there more prevalent among males than among females. Thus of 1,772 cancer deaths during the years 1879-89, 893 were males and only 879 females. Of 233 cancer patients under treatment at the Dunedin hospital during the same period, 140 were males and only 93 females.

It seems likely, if the disproportionate increase of cancer, among males, now going on in this country, continues unchecked, that the state of affairs in New South Wales and New Zealand will soon be paralleled here.

The relative proneness of females to non-malignant neoplasms and cysts is even greater than it is to cancer. This arises from the great frequency with which in women the reproductive organs, especially the uterus and ovaries, are attacked, the corresponding male organs seldom being affected.

We are so accustomed to regard the uterus as an essentially female organ that the very mention of the influence of sex, in matters of uterine pathology, seems paradoxical. It must be remembered, however, that men possess a rudimentary organ—the prostatic utricle (*uterus masculinus*), which is developed from the fused posterior ends of the Müllerian ducts, and is therefore homologous with a portion of the utero-vaginal canal. The great frequency with which cancers arise from the uterine mucosa, especially its lower part, is well known; but, in striking contrast with this, I cannot cite a single instance in which cancer has originated from the lining membrane of the prostatic utricle.

A somewhat similar state of affairs is revealed by a comparison of the relative proneness of the male and female mammæ to develop cancer; for of one thousand eight hundred and seventy-nine consecutive cases of this disease in the breast tabulated by me, only sixteen were in males.

In the foregoing cases we have a good illustration of the law, of which many other instances might be cited, that functionless, obsolete structures have but little tendency to take on the neoplastic process. It is evident from what has been stated, that we must seek for an explanation of these remarkable diversities in morbid proclivity, in biological peculiarities inherent to the affected parts; and in their concomitant developmental and structural diversities—all of which are ultimately ascribable to functional modifications—rather than to any general constitutional condition correlated with sex.

The Infuence of Age.

Malignant neoplasms of any kind are decidedly rare during early life, and fewer cases arise during infancy and childhood than at any other period. Of 941 consecutive malignant neoplasms under my own observation, only 25 (2.6 per cent.) commenced under the age of 20 years. Of these, 9 started in the first quinquenniad, 2 in the second, 6 in the third, and 8 in the fourth. The subject is further illustrated by the following table, showing the mortality from malignant disease at different age periods in England and Wales, during the year 1895.

Table I.—Showing the Deaths Due to Malignant Diseases at Different Age Periods.

Sex.	Under 1 Year.	1–2	2–3	3–4	4–5	5–10	10–15	15–20	20–25	25–35	35–45	45–55	55–65	65–75	75–85	Over 85.	All Ages.
Males...	12	10	20	11	7	33	39	51	65	227	642	1,653	2,546	2,349	881	82	8,628
Females	5	13	20	8	9	30	23	39	73	470	1,744	3,206	3,965	3,214	1,337	161	14,317

This shows that 1.43 per cent. of the cases originated under 20 years of age. It is sad to have to relate that, during the last decennium, the mortality from malignant disease in early life for the first time showed a decided increase, although the increment of increase was proportionally much less than at subsequent age periods. This is illustrated by the subjoined table from the registrar-general's recently issued decennial supplement.

TABLE II.—SHOWING THE NUMBER OF DEATHS FROM MALIGNANT DISEASE IN EARLY LIFE, PER MILLION PERSONS LIVING AT EACH AGE PERIOD.

Decennia.	Under 5.	5–10	10–15	15–20	20–25	All ages.
1861–70	13	7	7	7	17	384
1871–80	12	7	7	15	27	468
1881–90	20	10	11	20	35	589

A considerable proportion of these malignant neoplasms are undoubtedly congenital; that is to say, they originate during intra-uterine life. Moreover, they are often multiple *ab initio*, and not infrequently they are bilateral.

All tumors of this kind probably are sarcomatous; but many alleged examples of congenital "cancer" have been recorded. It must be remembered, however, that the sharp distinction now made between cancer and sarcoma is of comparatively recent origin. Many of the malignant tumors of infancy and childhood contain epithelial elements; and this has often led to their being christened "cancer." Numerous instances of this kind have been reported, especially in connection with the renal, testicular, ovarian, hepatic, gastric, and intestinal malignant neoplasms of early life. It is now generally recognized that the epithelial elements in such cases play only a secondary part, and that all such neoplasms really are sarcomatous.

In other examples of alleged "cancer" in early life the diagnosis has been based too exclusively on the microscopical appearances, the clinical features of malignancy being conspicuous by their absence. Instances of this kind have been published in connection with the lips, skin, external genitalia, etc.

In short, I conclude that infancy and childhood are completely exempt from true cancer, using this term in the sense of malignant epithelial neoplasm.

The earliest age at which cancer has been satisfactorily demonstrated is eleven years, the patient being a girl with cylinder-celled cancer of the rectum (Stern); and I have myself met with rodent ulcer in a young woman, in whom the disease began at the early age of fourteen years.*

In spite of a few exceptional cases of this kind, it may be safely asserted that under the age of puberty cancer is practically unknown.

The rectum is remarkable for the comparatively large number of cancers that arise from its mucosa during early life. Moreover, as previously mentioned, the earliest duly authenticated example of cancer hitherto recorded has been met with in this situation. More than a score of cases of rectal cancer, in which the disease originated under twenty years of age, might easily be cited.

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* For further information on this subject *vide* the article on sarcoma.

Such a state of affairs is, however, very unusual, for during the first four quinquennia of life most parts of the body are almost or quite exempt from cancer. This is the case with the mammæ; at least I know of no well-authenticated instance of mammary cancer that can be cited as having originated within this period. Alleged examples of it reported by Lyford (at eight years), Carmichael (at twelve), Cooper (at thirteen), Howe (at fifteen), etc., were never histologically verified; so we may safely assume that in these cases the disease really was sarcomatous, of which instances have been reported by Chambert at four months, by Vieregge in an infant, and by Gross at nine years.

Of five hundred consecutive cases of mammary cancer under my own observation, the youngest was twenty-four years of age; and of one thousand six hundred and twenty-two similar cases, tabulated by Gross, the earliest age at onset was twenty-one years (Henrys' case). The occurrence of mammary cancer before twenty-five is a great rarity.

In the uterus, cancer is hardly ever met with under the age of twenty years. Of five hundred consecutive cases of uterine cancer in my list, the earliest age at onset was twenty-two and a quarter years. By massing the statistics of several continental and English authors, Gusserow obtained a total of three thousand three hundred and eighty-five cases; and of this large number only two originated under twenty.

The earliest age at which the outbreak of uterine cancer has been duly substantiated is seventeen years; Schauta and Glatter have each recorded an instance of this kind, the cervix being the seat of the disease, which was glandular cancer. Mundé has reported a case at eighteen; Beigel and Tchop have each met with the disease at nineteen, and Billroth at twenty.

Several instances of so-called cancer of the uterus, at much earlier periods, have been recorded; but in none of them has the cancerous nature of the affection been satisfactorily established.

In Ganghofner's case of so-called cancer of the portio in a girl nine years old, the eroded papillary outgrowth was more like a non-malignant "cauliflower excrescence"—of which several instances have been met with in infancy—than cancer. The clinical history accords with this, for although the disease was of over two years' duration, it was localised and there was complete absence of dissemination.

The instances of so-called cancer of the uterus by Heckford at nine months, by Rosenstein at two years, by Laidley at two and one-half years, by Barnes at ten, by Simpson at twelve, and by Zweifel at thirteen years, were evidently sarcomatous.

In extreme old age, as in early life, cancer seldom originates. I have arrived at this conclusion by investigating the mortality from cancer of centenarians and aged persons of eighty years upwards. The information thus obtained shows that these aged persons are relatively much less prone to the disease than their juniors. This is shown by the following table which I have compiled from data contained in the registrar-general's reports for the years 1871–85:

TABLE III.—CENTENARIANS AND CANCER.

Year.	Deaths of male centenarians.	Deaths of female centenarians.	Total.	Cancer deaths.
1871	25	34	59	Nil.
1872	24	51	75	Nil.
1873	10	79	89	Nil.
1874	16	53	69	Nil.
1875	22	65	87	Nil.
1876	14	43	57	Nil.
1877	22	61	83	Nil.
1878	24	64	88	1 { A Chelsea pensioner, died aged 100, of "cancer."
1879	27	55	82	2 { A gamekeeper, died aged 100, of "cancer." A widow, died aged 100, of "cancer."
1880	20	48	68	1: a woman, died aged 102, of "cancer."
1881	25	66	91	Nil.
1882	17	54	71	Nil.
1883	12	35	47	1 { A woman, died aged 106, of "cancer of eye and wrist."
1884	18	40	58	Nil.
1885	19	44	63	Nil.
Total.	295	792	1,087	5 (males, 2; females, 3).

Thus of these 1,087 centenarians only 5 died of cancer, or 1 in 217; of 295 males 2 died of cancer, or 1 in 147; and of 792 females 3 died of it, or 1 in 264.

Humphrey's report on the maladies of old people is of similar import. Among 202 persons—males 92, females 110—ninety years of age and upwards, there was not a single instance of malignant disease; and of 622 persons—males 340, females 282—between eighty and ninety years old, there were only 14 instances of it. Thus of these 824 aged persons, malignant disease was met with only in 1.7 per cent., or in the ratio of 1 to 58.8; of 432 males, 7 were affected, or 1 in 61.7; and of 392 females 7, or 1 in 56. Of the males, the lip was the seat of the disease in 3 cases; the penis, ear, finger, and shoulder each in 1 case; of the females, in 5 the breast was affected, and in 2 the face.

These facts clearly show that cancer is *not* a senile disease; and that senility *per se* plays no essential part in its development.

The oldest cancer patient I know of is the woman referred to by the registrar-general, in his report for 1883, who died aged one hundred and six, with "cancer of the eye and wrist." Coker, of Chicago, has reported the case of a lady who died under his care, aged one hundred and six, of cancer of the tongue.

The oldest patient with mammary cancer seen by me was eighty-four when the disease commenced, and Bryant has met with an instance in which it began at the phenomenal age of ninety-six.

Of five hundred cases of cancer of the cervix uteri tabulated by me, the latest age at the onset of the disease was eighty-three years.

According to my estimate, the average age of women at the onset of mammary cancer is forty-eight years; whereas for uterine cancer it is forty-four; and for cancer of the tongue and mouth, fifty. The foregoing statement is based on the subjoined analysis of five hundred consecutive cases of breast cancer; and for the sake of comparison I have appended similar analyses of cases of uterine cancer, and of cancer of the tongue and mouth in women—all of them reduced to the percentage basis.

TABLE IV.—SHOWING THE AGE DISTRIBUTION OF CANCER OF THE BREAST, UTERUS, AND TONGUE.

Age periods.	Breast per cent.	Uterus per cent.	Tongue and mouth in women per cent.*
20 to 25 years	0.6	0.2	3
25 " 30 "	4.0	7.0	5
30 " 35 "	6.0	11.0	7
35 " 40 "	14.0	20.0	4
40 " 45 "	16.0	17.0	10
45 " 50 "	20.0	16.0	17
50 " 55 "	15.0	13.0	22
55 " 60 "	10.0	9.0	10
60 " 65 "	9.0	5.0	9
65 " 70 "	3.2	1.0	6
Over 70 "	2.2	0.8	7
	100.0	100.0	100.0
Mean age	48	44	50
Earliest age	24	22.25	24
Latest age	84	83	77.5

* Calculated on 90 cases.

In some of the other chief local forms of cancer the mean age at onset is as follows: For males—tongue and mouth 53.8 years, lip 51.6, rectum 50.7, mamma 50, œsophagus 56, stomach 51, penis 47.5, skin 58, rodent ulcer 44; for females—rectum 53.4 years, œsophagus 50.6, stomach 40.5, skin 45.8, rodent ulcer 42.7.

From the foregoing data, and from such as are set forth in Table I., we learn the absolute frequency of the disease at the various age periods; but, in order to ascertain the influence of age in its evolution, these figures must be compared with the total number of each sex living, at the corresponding age periods. The following table from the registrar-general's decennial supplement has been compiled on this basis. It shows that the mortality from cancer increases with each successive decade.

TABLE V.—SHOWING THE MEAN ANNUAL MORTALITY OF MALES AND FEMALES FROM CANCER, PER MILLION LIVING AT SUCCESSIVE AGE PERIODS DURING THE DECENNIUM (1881–1890).

Age periods.	Persons.	Males.	Females.
20 to 25 years	35	37	33
25 " 35 "	128	79	172
35 " 45 "	584	297	852
45 " 55 "	1,545	998	2,042
55 " 65 "	2,868	2,299	3,368
65 " 75 "	4,160	3,742	4,506
Over 75 "	4,295	3,914	4,578
All ages	580	430	739

In reference to such results Dr. Ogle remarks: "In simply saying that the liability to death from cancer increases with age, no more is said than may be stated with equal truth of liability to death generally. The question is, Does the annual liability to death from cancer increase more rapidly than the annual liability to death of all kinds?" To answer this question he has compiled the following table, showing the ratio of total deaths to deaths from cancer during the decennium 1871–80, at successive age periods.

TABLE VI.—TOTAL DEATHS TO ONE FROM CANCER.

Age periods.	Persons.	Males.	Females.
20 to 25 years	255	262	248
25 " 35 "	71	131	49
35 " 45 "	24	57	15
45 " 55 "	14	28	9
55 " 65 "	14	22	10
65 " 75 "	21	27	17
75 and upwards	48	56	44

It will be gathered from the foregoing that the characteristic feature of cancer mortality is not its increase with advance of years, but its disproportionate increase in the post-meridian periods. This table also shows very well the relative liability of the sexes at different ages. It will be noticed that the relative liability of females increases until the period forty-five to fifty-five, after which it lessens at each decade in a marked degree.

With regard to cancer of the female breast, statistics compiled on this basis by Paget and Nunn show that the period of its greatest relative as well as absolute frequency is between the fortieth and fiftieth years. Nunn's table, which was compiled for him by an actuary, is as follows:

TABLE VII.—SHOWING THE RELATIVE FREQUENCY OF MAMMARY CANCER AT THE DIFFERENT AGE PERIODS.

Age periods.	Per cent.	Age periods.	Per cent.
25 to 30 years	.831	60 to 65 years	9.696
30 " 35 "	3.933	65 " 70 "	9.181
35 " 40 "	8.783	70 " 75 "	4.983
40 " 45 "	12.311	75 " 80 "	3.923
45 " 50 "	18.006	80 " 85 "	3.824
50 " 55 "	16.161		
55 " 60 "	8.368		100.000

This shows that the relative liability of women to mammary cancer lessens progressively in a marked degree at each age period after fifty-five.

From what has been stated, it will be gathered that there is no such thing as congenital cancer, and under the age of puberty cancer is practically unknown. During the fourth quinquenniad a few cases may be met with, but its occurrence before twenty-five is a great rarity. In the third decennium more cases occur, but their number is still small. Subsequently they rise with increasing frequency up to sixty-five, when they attain their maximum. After seventy-five the disease is much rarer, and at more advanced ages the falling-off is still more marked until, in centenarians, it is as rare as in the fifth quinquenniad.

The period of maximum frequency is influenced by sex, for in females it occurs earlier than in males; in the former the period of greatest relative frequency being the decennium from forty-five to fifty-five, in the latter the decennium from fifty-five to sixty-five.

This difference is evidently due to diversity in localisation rather than to any general constitutional peculiarity correlated with sex; for the mean age at onset of uterine and mammary cancers is much earlier than that for cancer of other localities in women, the age of maximum frequency varying in diverse localities even in the same sex.

Attempts have often been made to ascribe the great frequency of cancer of the female reproductive organs to catamenial derangements. In this connection I have ascertained the following facts:

Of 100 uterine-cancer patients under my observation the disease was first noticed: before the menopause in 50; about the time of the menopause in 21; after the menopause in 29.

Of 87 women with mammary cancer the disease was first noticed: before the cessation of menstruation in 35; at about the time of the menopause in 10; after the cessation of menstruation in 42.

In the uterine-cancer patients the mean age at which menstruation began was 14.5 years, and at which it ceased 46 years.

In the breast-cancer patients the catamenia first appeared at 14.5 years, and ceased at 46.3 years.

Thus the flow is established earlier and ceases later in these cancer patients than in the generality of English women, in whom the catamenia usually begin at 15 and cease at 45.

Of 104 uterine-cancer patients menstruation had been normal in 96, and irregular only in 8 (scanty 6, profuse 2).

Of 87 women with mammary cancer the only catamenial derangements noted were profuseness in 6, irregularity and scantiness in 4.

These facts suffice to show that even in cases of uterine and mammary cancer the normality of the catamenial function is seldom disturbed; that it begins earlier and ceases later in them than in the generality of women is simply an indication of the more vigorous sexual life of cancer patients, which accords with other facts ascertained by me, relative to their life history, such as high fertility, early marriage, etc.

It is thus evident that the catamenial function has no causal connection with the development of cancer in women.

To sum up: We learn from the foregoing, that while the forces of growth, development, and reproduction are in greatest activity—during the periods of intrauterine life, infancy, childhood, adolescence, and adult age—the tendency to cancer is exceedingly small. In both sexes, the disease begins to be frequent as soon as the period of perfection has been attained, *i.e.*, after the thirty-fifth year; during middle age and the decline of life the liability to it increases, until about the sixty-fifth year; after which period it becomes markedly less frequent, and increasingly so as age advances. The principles that govern the age distribution of cancer in general, apply also to its various local manifestations in both sexes. That some parts of the body—such as the uterus and mamma—are attacked at an earlier age than others, is due to the fact that the former attain maturity earlier than the latter and *vice versa*. The general rule for the uterus, breast, and all organs is, that their liability to cancer begins with the decline of their functional activity, and increases while this is progressing.

Thus the liability to cancer waxes as the developmental and reproductive activities wane. The antagonism between the forces of genesis, growth, development, and expenditure is the same in pathology as in physiology. It is owing to the varied interactions of forces thus called into existence, that the constitution is so different at different periods of life, and that each period has its special morbid proclivities.

In this we have an illustration of the universal biological law that growth varies according to the surplus of nutrition over expenditure. So long as the surplus exists—that is to say, while nutrition is relatively high—simple *continuous* growth is maintained; but when nutrition is relatively low—that is to say, when it is nearly equalled by expenditure—new centres of development are apt to arise, and growth tends to become *discontinuous*. Changes of nutrition determine the transition from the one to the other mode of growth. To the operation of such causes, as I have elsewhere maintained ("The Principles of Cancer and Tumor Formation," 1888), the origin of cancers and other neoplasms must ultimately be ascribed.

COMPLEXION AND RACE.

The fact is well established, that when a number of individuals are exposed to the influence of similar conditions of life, all are not identically affected; and it is evident that the different effects thus induced depend upon inherent constitutional differences. In human beings well-marked constitutional peculiarities are correlated with complexion and race. I now propose to inquire whether the development of cancer is influenced by these. To this end I have noted the *complexion* of 384 cancer patients under my observation. In doing this I have relied chiefly on the color of the hair and eyes, as in white people these are its most permanent and easily recognizable factors.

MALES (128 CASES).

	Dark.	Fair.	Total.
Tongue and mouth....	30	28	58
Rectum	12	12	24
Lower lip	9	11	20
Skin	5	5	10
Tonsil	1	3	4
External genitalia	1	3	4
Rodent ulcer	3	..	3
Anus	3	..	3
Œsophagus	2	..	2
	66	62	128

FEMALES (256 CASES).

	Dark.	Fair.	Total.
Uterus..............	70	37	107
Breast...............	44	42	86
Rectum.	12	5	17
Rodent..............	5	7	12
Tongue and mouth...	4	4	8
Ovary...............	4	2	6
External genitalia....	2	3	5
Vagina..............	3	1	4
Œsophagus..........	1	2	3
Other localities......	5	3	8
	150	106	256

The numerical results thus obtained show that the majority of cancer patients (56 per cent.) are of the dark type; and it is to the female sex that this preponderance is almost exclusively due. In order to appreciate the significance of these results, we must first know the proportional frequency of the dark and fair types in the general population. Dr. Beddoe has most kindly furnished me with information as to this. His estimate shows that among the London lower classes 43 per cent. are of the dark, and 57 per cent. of the fair type. Hence it follows that cancer is relatively much more frequent among dark than among fair-complexioned persons, the proportion being, according to my estimate, 69 per cent. of the former to 31 per cent. of the latter. Beddoe's analysis nearly accords with this. He has also found that individuals of the rufous type are relatively less exempt than other fair-complexioned persons.

Here it may be remarked that the stress of life in large towns seems to exert a much more injurious influence on the fair complexioned—especially in early life—than on those of darker hue; owing to this cause it is believed that fair-complexioned types are gradually being supplanted in the large towns. Changes of this kind, which are very subtle and far-reaching, may be among the factors contributing to the greatly increased cancer mortality of modern times.

As to the influence of *race* in the liability to cancer, we have singularly little reliable information; but, so far as present indications go, it appears that all racial varieties of mankind are prone to the disease. According to United States statisticians (Billings, Barker, Chisholm), in that country cancer affects the whites much more frequently than the blacks (negroes).

The tenth United States census report shows that of 23,000,000 whites 6,321 died of cancer; whereas of 9,000,000 blacks only 790 died cancerous. That is to say, the deaths from cancer per 100,000 whites and blacks living were 27.96 and 12.17 respectively; for whites, the male death rate was 20.5, and the female death rate 35.4; for blacks it was for males 5.8, and for females 19.3.

We learn from numerous observers that this comparative immunity of the negro race from cancer, is even more noticeable in their African homes. Whether this is due to racial influence or to savage ancestry is not easy to decide. Those who have travelled among savage people are, however, unanimous in asserting that cancerous diseases are almost or quite unknown among them. This immunity applies alike to meat-eating and vegetarian savages. It should, however, be borne in mind that most uncivilised people get comparatively little animal food; or, at any rate, they often have to abstain from it for long periods.

On the other hand, it is certain that cancerous diseases are very prevalent in all highly civilised communities. Among the whites in the United States, the census reports show that those of French, English, German, and Irish extraction are the most prone to cancer; which is of more frequent occurrence among the foreign-born whites than among those born in the country. This last peculiarity has also been noticed in Australia.

In all parts of British North America cancer is fairly common among whites. In Canada, Landry (1861) found that it was of common occurrence among all the various peoples, except the aborigines.

It has been asserted that the Jews are seldom affected, but in this, Richardson—who has had considerable experience among them—does not agree; Billroth's experience coincides with this; and Billings' reports show that in the United States their death rate from cancer is almost the same as that of the rest of the white population. Moreover, from observations made by Bauby in the neighborhood of Toulouse, it appears that pork-eaters are no more prone to cancer than those who feed on other kinds of meat.

GEOGRAPHICAL DISTRIBUTION.

Notwithstanding the interest lately manifested in the geographical distribution of cancer, of accurate scientific information there is rather a dearth. In tropical and arctic regions the disease is said to be very rare.

Statistical records have been kept only in Europe, the United States, and some of our colonies. These show the much greater prevalence of the disease in Europe. According to the eleventh United States census report (1890) the cancer mortality for the whole country then amounted to 3.19 per 10,000 living, or 24 per 1,000 (1 in 41) of the total deaths.

For the chief European countries the cancer death rates per 10,000 living are: Sweden (1886–87) 9.5, Saxony (1876–85) 6.9, Netherlands (1884–88) 6.5, Italy (1881–83) 6.1, England and Wales (1881–90) 5.89, Scotland (1885) 5.6, Norway (1862–66) 5.2, Austria (1885–87) 4.8, Italy (1887) 4.2, Ireland (1885) 3.9, Prussia (1876–85) 3.4.

I have not met with any recent statistics showing the mortality from cancer in France; but Lombard, writing in 1880, says it is much in excess of the English mortality. In Denmark and Switzerland cancer is very prevalent. From such scanty data as come to hand from Russia, the disease appears to be fairly common there. In Turkey and Greece cancer is said to be very rare, but this needs confirmation.

In the large cities of the United States the cancer mortality in 1890 was as follows: Boston 7.9, Baltimore 6.5, New York 6.2, Philadelphia 5.5, Washington 5, and Brooklyn 4.8; in 50 large United States cities (*circa* 1880), males 2.8, females 5.1.

For some of the chief European cities the numbers are as follows: Lyons (1892) 16.3, Rouen (1890) 12.7, Paris (1886–91) 10.4, Rheims (1890) 10.1, the chief Danish towns (1886–87) 10.9, Edinburgh (1892) 9.3, Aberdeen (1892) 8.9, Dundee (1892) 8.3, London (1881–90) 6.8, Glasgow (1889) 6.1, Bremen (1875–78) 8.1, Hamburg (1871–83) 7.6, Berlin (1870–82) 5.7, Bergen (1886–87) 5.4, Christiania (1886–87) 5, Utrecht (1870) 4.9, and Brussels (1890–94) 3.6.

The cancer mortality of Geneva, Frankfort, and Breslau is very high, while St. Petersburg has a lower cancer death rate than Berlin.

Continental statistics indicate much greater frequency of the disease in the stomach, intestines, and liver than British ones. Chimney sweep's cancer, rare even in England, is hardly ever met with elsewhere.

Cancer is said by Panum to be unknown in the Faröe Islands, and to be exceedingly rare in Iceland (0.7 per 10,000 persons, *circa* 1880). Dr. Russel-Jeaffreson, who has recently visited these islands, informs me that cancer is still very rare there. In the Faröe Isles he himself never saw a case, but the resident doctors told him that the disease was occasionally met with, generally in half-breeds and Danish immigrants. In both islands tuberculous diseases, including phthisis, are rare.

In Greenland cancer is said to be as rare as in Iceland.

As we get to know more about remote localities, it will probably be found that no settled community is completely exempt from cancer.

Of Asiatic countries it is generally agreed that cancer is most prevalent in China; and, according to Hobson, the female breast is frequently affected. Desiring to obtain recent information on this subject, I lately wrote to Dr. Cantlie, of Hong-Kong, who kindly furnished me with the following particulars, for which I now thank him. Referring to the prevalency of the disease he says: "I do not think I have been without a case of malignant disease under my care ever since I came to China six years ago." Of 3,608 consecutive Chinese hospital in-patients under his care, 114 had cancer, or 3.1 per cent. This proportion is almost identical with that met with in large London general hospitals, like St. Bartholomew's, where 3.5 per cent. of the in-patients have cancer. Of Cantlie's 114 Chinese cancer patients, the primary seats of the disease were as follows: female breast, 38; upper jaw, 25; lower jaw, 14; penis, 9; uterus, 8; parotid gland, 5; hip, 5; tongue, 4; lip, 3; and thigh, 3. At Dr. Kerr's hospital in Canton, during the year 1887, 30 cases of malignant disease were operated on, including 11 amputations of the female breast. Strange to relate, Cantlie has never met with cancer of the stomach among the Chinese. With regard to their diet he says: "All Chinamen eat fish and pork at morning and evening meals. Fowls and ducks are always on the table of all but the most humble of the coolie class; and they do not have them because they cannot afford them. I hope this will be a sufficient answer to those who maintain that Chinamen live on rice. It is not nearly so true as that the Scotch live on porridge."

In India cancer is said to be rare; but neither the rice-eating Hindoos, nor the flesh-eating Mohammedans are exempt. In support of the alleged rarity of cancer in India, Davidson mentions that of 2,657 operations performed at the Afzulgung Hospital at Hyderabad in 1886, only 2 were for cancer; while in Bombay only 1 per 1,000 of the total deaths were ascribed to it. On the other hand, McLeod states that malignant neoplasms (cancer and sarcoma) are common among the natives of Bengal, both in hospital and private practice; in females the breast being chiefly affected, and in males the cutaneous system, oral cavity, and especially the penis. Hendley's experience at the Jeypore Hospital seems to accord with this, for during the period 1880–88, when the hospital was under his charge, 102 major operations were undertaken for the treatment of malignant disease. As—in the face of these conflicting statements—further information seemed desirable, I wrote to Surgeon Lieutenant-Colonel Lawrie, of Hyderabad, who kindly favored me with the following reply:

"My experience of cancer is, that it is as frequent in India as in England; and I have formed this opinion from observation in Calcutta, Lahore, and Hyderabad. The Afzulgung Hospital was under my charge in 1886, and that year was no exception to the rule. The small number of operations for cancer shows nothing, except that the people are averse to operation for most diseases, other than stone and cataract."

With regard to the prevalence of malignant disease in the vast northwestern provinces and the Punjab, I am indebted to Dr. Freyer for the following information. He writes: "The general impression on my mind, after seventeen years of active surgical work among the poor and rich of India (northwestern provinces mainly), is that tumors of all kinds, including cancer and sarcoma, are extremely common. Epithelioma of the tongue and penis, and scirrhus of the breast are particularly common."

Four-fifths of the inhabitants of these provinces are Hindoos, who, with few exceptions, in accordance with the precepts of their religion, never eat meat. The other fifth, being Mohammedans, may eat meat, but they are practically vegetarians, as they can seldom afford the luxury of animal food. Among these people stone is extremely common.

In Cashmere, Orissa, Madras, Anam, and Çochin, cancer is said to be more prevalent than in adjacent communities.

In Syria, Persia, and Arabia, according to Lombard, the disease is very rare.

No part of the world is reputed to enjoy such relative immunity from cancer as Africa; this applies to nearly all parts of the continent, but especially to its northern part, Egypt, Tunis, Algiers, etc. In order to ascertain the present state of things in Egypt, I lately wrote to Dr. Engel Bey, of Cairo, who very obligingly sent me the following data. Of 19,529 deaths among natives in Cairo during 1891, only 19 were returned as due to cancer (females 10, males 9), or 1 in 1,028; in England during the same year, the proportion of cancer deaths was 1 in 29. Of 12,950 patients in the Kasr-el-Aini Hospital, during the years 1889–91, 77 were affected with cancer, or 0.6 per cent.; whereas in metropolitan general hospitals I have ascertained that the proportion of cancer cases is about 3.5 per cent. From these data it appears that the reputation of Egypt for comparative immunity from cancer is well founded.* With regard to the prevalence of cancerous diseases in Morocco, I am indebted to Mr. Ernest Hart for the following valuable information. In answer to my letter of inquiry, he very kindly wrote to Dr. Terry, of Tangiers, who replied as follows: "Cancers, sarcomas, etc., do not seem to be very prevalent; at any rate the number of cases met with, as compared with other diseases, shows that they are of less frequent occurrence than in England. Among the inhabitants, who are of mixed Arab and native blood, I have seen cancers of the female breast, uterus, and tongue; as well as sarcomatous growths in various parts of the body."

Legrain has lately called attention to the rarity of cancer among the aborigines of Algeria, which he ascribes to their abstinence from animal food and intoxicating drinks. Kirmisson states that of 5,561

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* In Egypt insanity is phenomenally rare; but there is a fair amount of tubercular disease, including phthisis.

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deaths in Algeria (1852–54) only 37 were due to cancer, or 1 in 150.

During his recent visit to Somaliland and Erythrea, Fiaschi was struck with the absence of cancer among the crowds who flocked to his clinic, although tuberculous and syphilitic affections were common.

At the Cape, cancer is common among the whites, but very rare among the natives, who are mostly vegetarians.

Livingstone speaks of cancer as being absent from the Barotze valley and among the Bakwains, although the latter are prone to fatty and fibrous tumors.

In Abyssinia cancer is said to be commoner than in any other part of Africa.

As to the relative frequency of cancer in South American countries, we have singularly little definite information.

Its presence is well recognized in Brazil, Montevideo, Ecuador, and Peru. Of 13,725 deaths at Rio de Janeiro in 1890, 123 were due to cancer, or 1 in 111, and 2,200 to tubercle.

According to Journdanet it is almost unknown in the hot regions of Mexico, while in the high cool regions it is as frequent as in Europe.

In British Guiana three per cent. of the total hospital deaths in 1888 were due to cancer.

The disease is rare in Jamaica (1.19 per 10,000 living in 1888), and in Mauritius (0.6 per 10,000 living).

In Australasia cancer is common, especially in Victoria and Tasmania, but less so than in England.

The following are some of the chief death rates per 10,000 living: Victoria (1891) 5.5, Tasmania (1891) 5.0, New Zealand (1891) 4.4, New South Wales (1892–94) 4.16, South Australia 4.0, West Australia (1882–86) 3.6, Queensland (1891) 2.9.

In Australia, as in the United States, cancer is more prevalent among immigrants than among those born in the country. According to Mullins, among the British-born Australians 1 in 966 die of cancer, whereas among the Australian-born the mortality is only 1 in 7,746.

Topography.

In every part of the world the distribution of cancer presents many topographical variations. Moore was one of the first to study these for England and Wales. He showed that the disease was more prevalent in London and the adjacent southern and eastern counties than elsewhere; and that it was least prevalent in Wales and in the northwestern (Lancashire) and northern counties. If, he says, the country be divided by a line from Bristol to Peterborough—which practically separates the industrial from the agricultural communities—the mortality from cancer in the southern divisions is considerably in excess of that on the north of the line. In the year 1861, for instance, one of every thirty deaths of women in the southeastern (agricultural) division was due to cancer; while the deaths of women from cancer in the northwestern (industrial) division were only about half as many, or one in fifty-nine of the total female mortality.

The subjoined table from the registrar-general's forty-seventh annual report (1886) shows the cancer mortality in the chief registration divisions during the thirty years 1851–80.

MEAN ANNUAL MORTALITY PER STANDARD MILLION, AGED 25 AND UPWARDS.

	Males.	Females.	Persons.
England and Wales (average)	561	1,144	867
London	736	1,463	1,117
Southeastern	557	1,207	898
South-Midland	597	1,148	886
Eastern	502	1,175	855
West-Midland	519	1,133	841
Yorkshire	511	1,114	827
Northern	565	1,041	815
Southwestern	555	1,043	811
Northwestern	523	1,055	802
North-Midland	496	1,074	799
Wales	538	841	697

The results brought out by this table are identical with those established by Moore, and data published in the recently issued decennial supplement (1881–90) show that these variations in local incidence still persist.

Counties with the highest cancer death rates are: London, Cambridgeshire, Huntingdonshire, Northamptonshire, Sussex, Warwickshire, Beds, Surrey, Middlesex, etc. Those with the lowest are Derbyshire, South Wales, Bucks, Herts, Durham, Cornwall, Monmouthshire, Dorsetshire, Lancashire, etc.

Provincial towns having the highest cancer mortality during the decennium 1881–90 are: Chichester (11.8 per 10,000 living), Canterbury 11.3, Bala 10.7, Huntingdon 10.6, Exeter 10.1, Saffron-Walden 9.9, Cambridge 9.5, Bath 9.5, Buckingham 9.4, Holbeach 9.2, etc. It is noteworthy that this list does not include a single great industrial centre, the places named being well-to-do, easy going, sleepy country towns.

By noting the birthplaces of three hundred and fifty-two cancer patients I have ascertained that the localities of greatest cancer mortality are also the localities where most cancer patients are born.

It is a matter of importance to determine the part played in the causation of these local variations in the cancer mortality, by differences in the age and sex distribution of the population; but unfortunately the requisite data for making corrections of this kind are seldom available. The registrar-general has, however, lately published estimates of the cancer mortality of the chief English counties, corrected for age and sex distribution. From these it appears that while the accuracy of the general results indicated by the crude death rates is not impugned, the comparative mortality of individual counties *inter se* is disturbed by the corrected computation; for instance, while the crude cancer death rate of Huntingdonshire to that of Durham is as 208 to 100, the corrected death rates are as 127 to 100—yet the former county still retains its status as one of the districts where cancer is most prevalent, and the latter as one of those where it is least so.

It is thus evident that there are topographical variations in the incidence of the cancer mortality, which are quite independent of age and sex distribution.

The average age of the Irish population, for instance, is much higher than that of either England or Scotland; and the proportion of elderly women it contains is also greater, owing to the large numbers of elderly people left behind after the younger ones have emigrated; yet the cancer mortality of Ireland is much less than that of either England or Scotland. This clearly shows that inequalities in the incidence of the cancer mortality are determined by other considerations than those of mere age and sex distribution.

Hence, it is exceedingly improbable that the higher cancer mortality of the rural, as compared with the industrial, population can be explained as the result of diversity in the age and sex distribution of the respective populations, although such diversities certainly exist.

According to Haviland, these variations are entirely due to geological configuration and its consequences. He maintains that the regions of highest cancer mortality are low-lying districts, traversed by, or contiguous to, rivers that seasonally flood the adjacent riparial lands; whereas the lowest cancer mortality is found in high and dry sites, where floods do not occur, and where the subsoil consists of hard, non-retentive rocks (*e.g.*, English lake district) or of absorbent substances like chalk and oölite. In support of these views, he instances the Thames and its tributaries, which run through a vast cancer-field; and he points to the only localities in the Thames valley—the Orsett and Dartford districts—where there is a low cancer mortality, as being just those spots where the chalk crops out.

In favor of the opinion that, in this country, cancer is specially prevalent in flat, low-lying, fenny districts, there is, I think, much to be said. The forty-seventh report of the registrar-general shows that Cambridgeshire and the adjacent counties of Northamptonshire, Huntingdonshire, and Bedfordshire, all have a very high cancer mortality. Lincolnshire and Essex figure less prominently in this report; but my analyses show that the number of cancer patients born in these localities is exceedingly high. This state of things is known to have existed ever since statistical records have been kept. In the decennial report (1881–90), the registrar-general—writing on this subject—says: "Crude death rates show that in and around Huntingdonshire and Cambridgeshire there is a well-defined area in which cancer is exceptionally prevalent. It comprises the districts of Stamford, Bourn, Spalding, and Holbeach in Lincolnshire; Oundle and Peterborough in Northamptonshire; and most of the counties of Huntingdonshire and Cambridgeshire. In 1881–90 this area had a mean population of over 300,000, its crude cancer rate being 859 per million, or 46 per cent. above the average rate for the country in general; in the preceding decennium the excess was 44 per cent."

Nevertheless, I am unable to accept Haviland's views as a sufficient explanation of the topographical variations in the distribution of cancer. All low-lying and seasonally flooded districts have not a high cancer mortality; the very large area drained by the Severn and its tributaries, for instance, is shown by the registrar-general's forty-seventh report to have a low average cancer mortality.

Moreover, many islands that have no rivers, that are not low-lying, and that are not of alluvial formation, nevertheless have a very high cancer mortality; such are the Scilly and Channel Islands and the Isle of Wight. The Scillies are small and rocky throughout; their total population is under 2,000; but, during the decennium 1881–90, their cancer death rate was considerably higher than that for all England. The respective data per 10,000 living are as follows:

	Persons.	Males.	Females.
Scilly ...	7.6	2.9	12.2
England...	5.8	4.3	7.3

Similar conditions are met with in many inland districts. Thus Dr. Borrowman, of Elie, in Fifeshire, N. B., writes to me: "It will interest you to know that cancer is very common here. Between 11 and 12 per cent. of my patients have died from malignant disease. This is a particularly dry part of the country. There are no rivers at all in the district; and the few streams that do exist have a good fall. Flooded land is quite unknown here."

As I have elsewhere pointed out the futility of the recent attempts to explain these topographical variations as the outcome of contagion, I need not further dwell upon this matter here.

It appears to me that it is in the conditions of life peculiar to the respective populations this explanation must be sought.

Generally speaking the cancer mortality is lowest where the struggle for existence is hardest, the density of population greatest, the tubercle mortality highest, the average duration of life shortest, the infantile and general mortality highest, and where sanitation is least perfect—in short, among the industrial classes; whereas, among the wealthy and well-to-do—where the standard of health is at its best and life is easiest—and among the agricultural community, there the cancer mortality is highest. Other things being equal, there are, in my opinion, no more potent factors in the causation of cancer than high feeding and easy living. Hence it is that the cancer mortality of mining and industrial centres like South Wales, Lancashire, Durham, Cornwall, West Riding, etc., is so low; and that it contrasts so favorably with the cancer mortality of the generality of agricultural districts. Although the ratio of pauperism in the rural districts is quite double that of the industrial ones, I have no hesitation in saying, as the result of my own observation of life under both conditions, that so far as food and comfort are concerned, the agricultural laborer is much better off than his more highly paid *confrère* of the industrial army. As a proof of this it may be mentioned that the average duration of the agricultural laborer's life is more than double that of his mate in the large towns.*

On the other hand, in London and the home counties, where the wealth of the nation is clotted, there the cancer mortality is highest; and it is a significant fact that this mortality is highest of all in those parts of the metropolis where the well-to-do most abound. The cancer mortality of West London is double that of the East End.

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* On this subject a leading newspaper lately remarked: "The material prosperity of the agricultural laborer is, and has been, during recent years, higher than at any period during the last century. The slight falling-off in the amount of his wages is more than compensated for by their increased purchasing power. All the necessaries of life, within the last thirty years, have become much cheaper—meat, bacon, cheese, tea, sugar, butter and coals—the difference being something like 25 per cent. in favor of the buyer. (Standard, August 12th, 1897.)

This is illustrated by the following data from the registrar-general's last decennial report (1881–90):

		Persons.	Males.	Females.
All England		5.8	4.3	7.3
London		6.8	5.0	8.4
Wealthy Districts.	Chelsea	14.9	9.1	20.1
	Marylebone	12.0	8.7	14.6
	St. George's, Hanover Square	9.6	8.5	10.6
	Paddington	8.9	7.5	9.9
	Kensington	8.1	6.7	9.0
Industrial Districts.	Stepney	3.7	2.5	5.0
	West Ham	4.0	2.6	5.3
	Bethnal Green	4.2	3.3	5.0
	St. Saviour's, Southwark	4.7	3.0	6.3
	Mile End	4.8	2.4	7.0
	St. Giles'	4.8	3.0	6.4
	Shoreditch	5.2	3.8	6.5
	Poplar	5.1	3.9	6.3
	St. George's in the East	5.4	3.7	7.1
	Whitechapel	11.8	11.3	12.4

To make these data perfectly reliable for determining the incidence of cancer, no doubt they ought to be corrected for age and sex distribution; and also for the presence of large hospitals. It is probably largely owing to the latter cause that the cancer mortality of Chelsea, Marylebone, and Whitechapel is so abnormally high. But when allowance has been made for all such modifying conditions, it is still evident that the cancer death rates of the industrial districts are very much lower than those of the districts where the wealthy and well-to-do reside; moreover, a similar state of things is noticeable in other large towns, and throughout the country in general.

In most countries similar topographical variations are met with. In the United States the disease is much more prevalent in the Northern than in the Southern States. It is especially frequent in New England, the southern part of the Pacific coast, in New York, Pennsylvania, Ohio, and Michigan. The areas of its least prevalence are the Mississippi valley, and the Southern States. Many of these irregularities are probably largely due to racial peculiarities.

In France cancer is unduly frequent in Lyons and its vicinity, and in Paris, and lately a great deal of attention has been given to the frequency of its occurrence in certain Normandy villages.

In Prussia, the disease is commonest in Schleswig-Holstein.

Family History.

HEREDITY OF CANCER.

The problem of heredity in relation to disease has hitherto seldom been viewed in a right light. The fundamental error has been the tacit assumption that pathological states, like normal conditions, are almost invariably inherited. It has been overlooked that the predispositions of the organism are to normality; and that diseases—like other recently acquired characters—tend to disappear under suitable environmental conditions. In fact, so great is the preponderating influence of the previous ancestral balance that diseases are never reproduced in the offspring with the same constancy and regularity that normal conditions are. Hence, even in families where hereditary morbid tendencies are the strongest, most of the members usually escape; and this is notably the case with cancer.

Nevertheless it is undoubtedly true that the descendants of an individual in whom a new morbid variation has appeared are, other things being equal, more likely to vary again in a similar way than are persons whose ancestors have never manifested such variation. This principle, as I shall proceed to show, is also applicable to cancer.

Very conflicting are the views now prevalent as to the *hereditability* of the disease. On the one hand there are those who regard this as an impossibility; and on the other, those who cannot conceive an explanation of cancer without it. These contradictory opinions are no doubt largely attributable to the prevailing confusion in the fundamental conceptions of heredity. As I cannot here enter on the burning question of Weismannism *versus* Darwinism, it must suffice for me to state that I regard the distinction between somatic and germ cells, on which Weismann's theory is based, as artificial. I believe that the reproductive properties manifested by somatic and germ cells are the same in kind, and that they differ only in degree.

The first principles being in this unsettled state, it will be well to pass at once to the consideration of the cardinal facts.

To my mind the hereditability of cancer is more conclusively proved by the occurrence of several instances of the disease in certain families, in one or in successive generations, than by any other consideration. Although such coincidences may not invariably furnish absolute proof of hereditary transmission; yet, when we see families thus affected, in which neoplasms of the same kind, develop in the same organs, and that during several generations, it seems to me impossible to deny the hereditability of the disease—especially when, as is so frequently the case, these morbid manifestations are exclusively confined to one side of the family.

Such instances of multiple family cancer as the subjoined prove the hereditability of the disease; for it is obviously impossible that those thus affected could have acquired the malady from a common source of infection, and the concurrence cannot be interpreted as a fortuitous occurrence.

1. I have known a woman, aged fifty-three, with uterine cancer, whose maternal grandmother, mother (aged forty-five), mother's sister, and the patient's two sisters (aged thirty-two and thirty-six), had all died of cancer of the *uterus*. She was one of a family of eleven; of her other brothers and sisters, three died in infancy, and five were still alive and well.

2. Atthill mentions the case of a woman, aged twenty-eight, with *uterine cancer*, whose mother and two sisters also died of cancer of the same organ.

3. In a case recorded by Sibley, the mother and her five daughters all died of cancer of the *left breast*.

4. Of the celebrated Bonaparte family, Napoleon I., his father, his brother Lucien, and two of his sisters, Pauline and Caroline, all died of cancer of the *stomach*.

5. Manichow reports that 23 families known to him in "la Soissonnais"—where consanguineous marriages are frequent—had between them 69 cancerous members; and of these in no less than 57 the *stomach* was the part affected; of the other 12 cases, in 4 the disease was situated in the uterus, in 3 in the breast, in 3 in the rectum, and in the bladder and liver each in one case. This is a striking instance of the preponderant frequency of homotopic transmission in the related individuals.

6. The following case, recorded by Broca, is the most complete of its kind that has ever been published; and this is mainly due to the fact that the family included an eminent physician among its members, who furnished the particulars as under:

First Generation.—Madame Z. died of cancer of the breast (1788), aged 60. She left four daughters—A, B, C and D.

Second Generation.—The four daughters of Madame Z.—

(1) Madame A. died of cancer of liver, aged 62 (1820).
(2) " B. " " " " 43 (1805).
(3) " C. " " breast, " 51 (1814).
(4) " D. " " " " 54 (1827).

Third Generation.—Madame A. had three unmarried daughters, who are still alive and well, aged 68, 72, and 78 years.

Madame B. had five daughters and two sons. First son died—not cancerous—at the age of 28, and without issue. Second son died of cancer of stomach, aged 54, and without issue.

First daughter	died of cancer of	breast,	aged 35	All unmarried, and without issue.
Second	“ “	“	“ 35–45	
Third	“ “	“	“ 35–45	
Fourth	“ “	liver,	“ 35–45	
Fifth	“ died, not cancerous, aged 60, married, but no issue.			

Madame C. had five daughters and two sons:

First son died in the army, without issue.	
Second son alive and well, aged 72.	He had a son who died paraplegic, aged 18; and an only daughter, who is now alive and well, aged 24, unmarried.
First daughter died of cancer of the breast, aged 37, leaving two sons and three daughters.	First son, aged 58, alive and well. He has three sons alive and well—the oldest 30. Second son died young, abroad, without issue. First daughter died in child-bed, about 28. Second daughter died of cancer of the breast, aged 49. She left two daughters; both are alive and well; the elder is now 22. Third daughter died of phthisis, aged 41.
Second daughter died, aged 40, of cancer of the breast.	She left an only son, who is still alive and well.
Third daughter died, aged 47, of cancer of the uterus.	Unmarried.
Fourth daughter died, aged 55, of cancer of the breast.	She left two sons, who are alive and well.
Fifth daughter died, aged 61, of cancer of the liver.	Unmarried.

Madame D. had an only son, who is alive and well, aged 70.

7. In a case lately recorded by Power, the patient was a man with recurrent inoperable cancer in the axilla. Two years previously his right *breast* had been extirpated for the primary disease, which subsequently recurred in the axilla, whence it was extirpated a year ago. His father died of cancer of the left breast. Of his two brothers and eight sisters, all but two of the latter, who died young, have developed cancer. Of his brothers the elder died aged 65 of cancer of the throat; and the younger, aged 24, of cancer of the left axilla. Of the sisters, four have died of cancer of the breast; and the two now living both have cancer of the breast.

Of my 136 mammary-cancer families, there was a history of the disease in more than a single member in 8: in 1 family 7 members were affected, in another family 4, and in 6 families 3 members were affected.

A remarkable feature about many cases of inherited cancer is that the disease, like normal structure, is often homotopic in its transmission; that is, it attacks the corresponding organ in each of the related individuals. This is especially noticeable in Sibley's case, where the mother and her five daughters all had cancer of the *left* breast. Although this form of transmission often defaults, it is nevertheless noteworthy that, on the average—taking all the seats of inherited cancer into consideration—homotopic transmission preponderates. Thus, of the 48 seats of inherited cancer, in my analysis of the family history of 136 cases of mammary cancer in women, the breast was the organ affected in 19; similarly, of the 15 seats of the disease inherited from Madame Z. who had mammary cancer, in 9 the breast was affected; and of the 32 seats of hereditary disease, noted in my analysis of the family history of 142 uterine-cancer cases, in 13 the uterus was the part affected. The tendency to homotopic transmission may thus be taken as the established rule, although the number of cases in which heterotopic transmission occurs is by no means inconsiderable. I can discover no ground for the dictum that homotopic transmission is especially apt to prevail among near relatives, and heterotopic transmission among distant ones.

In other varieties of tumors similar conditions are met with; thus there has lately been reported an example of melanotic sarcoma of the left eyeball in three generations (Silcock); two brothers with sarcoma of the left kidney (Strümpell); three sisters with bilateral ovarian cystoma (Löhlein); and Otto cites an instance of four brothers and sisters who all died of malignant disease of the eye.

Some remarkable instances of the hereditary transmission of melanosis in horses are cited by Virchow. In one of these a young white stallion, with melanosis of the anus, transmitted this disease to all its white descendants, while those of darker color escaped. From horses thus bred the disease became widely diffused through the neighboring country.

From the foregoing facts it may be inferred that the molecular protoplasmic disturbance, which eventuates in inherited malignant disease, affects the whole of the archiblastic or parablastic tissues of the body, as the case may be; but that its influence is most felt in that part which corresponds to the seat of the disease in the ancestor. Such indications point to intrinsic rather than to extrinsic causative conditions.

Analysis of the records of the family history of over 700 cancer and tumor patients, in order to ascertain the frequency with which there was a history of heredity, yields the following results: Of 124 uterine-cancer cases, there was history of heredity in 28 (19.7 per cent.). Of 136 cases of mammary cancer, there was history of heredity in 33 (24.2 per cent.). Of 92 other female cancer cases, there was a history of heredity in 22 (23.9 per cent.). Thus of these 370 female cancer patients, there was a history of heredity in 83 (22.4 per cent.).

From whatever point of view the subject is regarded, this is a very high percentage. Many anomalies, well known to be hereditary, yield on inquiry a much lower proportion; for instance, of 92 cases of supernumerary mammary structures analysed by Leichtenstern, there was history of heredity in only 7, or in 7.6 per cent. In my opinion, data such as the above, are of themselves presumptive evidence of the hereditability of cancer, for it is certain that no such great proportion of cancerous relatives is to be found among the relatives of the non-cancerous.

Of 209 men suffering from cancer, there was a history of heredity in only 23 (11 per cent.). I attribute this difference to the fact that the men knew so much less than the women of the details of their family history.

There was a history of the inheritance of cancer, *directly from parents,* in about 8 per cent. of the total cases.

My analysis of the family history of 136 mammary-cancer patients shows that the relatives thus affected and the seats of the disease were as follows:

Father's father (in two families)	Nose. Œsophagus.
Father's mother (in two families)	Breast. Breast.
First cousin of father's mother (in one family)	Œsophagus.
Father (in five families)	Breast. Lip. Hand. Internal. Liver.
Father's sister (in ten families)	Breast (5). Mouth. Face. Scalp. Liver. Internal.
Mother's mother (in three families)	Breast. Uterus. Locality not stated
Sister mother' father (in one family)	Breast.
Mother (in seven families)	Uterus (2). Stomach. Breast. Tongue. Internal (2).
Mother's sister (in six families)	Breast (4). Internal. Tongue.

Mother's brother (in one family)	Groin.
Female cousin on mother's side (in two families)	Breast. Locality not stated.
Patient's sister (in five families)	Breast (3). Uterus. Locality not stated.
Patient's brother (in two families)	Throat. Back.
Patient's daughter (in one family)	Internal.

These 48 seats of hereditary disease may be grouped thus: breast 19, internal 6, uterus 4, liver 2, œsophagus 2, all others 15. In 8 cases more than a single relative was affected, and in 4 cases there was history of cancer in the families of both parents.

The records of the family history of 142 consecutive cases of uterine cancer yielded the following results:

Father's brother (in one family)	Face.
Father's brother and three cousins (in one family)	Stomach (brother). Breast (female cousin). Neck (male cousin). Foot (male cousin).
Father's sister (in three families)	Uterus. Intestine. Arm.
Maternal grandmother (in one family)	Uterus.
Mother (in nine families)	Uterus (2). Breast (2). Stomach (2). Intestine. Abdomen. Face.
Mother's sister (in six families)	Uterus (2). Breast (2). Locality not stated (2).
Mother's brother and child of mother's sister (in four families)	Stomach (brother). Face (brother). Stomach (sister's child). Locality not stated (brother).
Patient's sister (in eight families)	Uterus (6). Breast (2).
Patient's brother (in one family)	Stomach.
Patient's daughter (in one family)	Uterus.

These 38 seats of hereditary disease may be grouped thus: uterus 13, breast 7, stomach 6, face 3, locality not stated 3, intestine 2, abdomen, arm and foot, each 1.

In two cases more than a single relative was affected: in one of these families all the affected relatives were on the mother's side, and in the other all were on the father's side.

In physiological heredity it is a generally accepted rule that the descendants of an individual in whom a new variation has appeared are—other things being equal—more likely to vary again in a similar way than are persons whose ancestors have never manifested such variation. That the same tendency, in a less degree, holds also for pathological heredity I have not the slightest doubt, although in the case of cancer attempts have been made to prove the contrary by ingenious statistical computations. ' This opinion is based upon the following evidence:

1. That derived from the study of multiple family cancers. Thus, in Broca's celebrated case, of the 26 descendants of Madame Z. who attained or exceeded the age of thirty, 15 died of cancer; whereas the cancer mortality for the same number of persons of the general population, at the corresponding period of life, is considerably less than 1; that is to say, the liability to the disease was increased more than fifteen times by the influence of heredity.

2. That derived from comparing the proportion of cases with family history of cancer among the cancerous and the non-cancerous. Thus, of my 370 female cancer patients there was a history of cancer in 83 families, or in 22.4 per cent.; whereas of 101 cases of non-malignant tumors and cysts in women there was a history of cancer in only 16 families, or in 15.8 per cent. Hence in these cases the liability to the disease was increased nearly 8 per cent. by the influence of heredity. The above data were collected by myself, and the inquiries were equally carefully carried out in both sets of cases.

Of 147 patients with non-malignant neoplasms, whose family history was analysed by Paget, only 6.8 per cent. were aware of having had cancerous relatives.

The phenomena of inheritance teach us that the actual product of a fertilized germ never represents the full measure of its potentiality. Only a portion of the many varying tendencies inherited by the reproductive cells, from their long line of ancestors, are actually evolved in each generation. Hence, in normal heredity, we constantly see transmitted besides developed structures certain tendencies and predispositions. Thus the male and female secondary sexual characters are transmitted through each sex, though usually developed in one alone. Similarly, tendencies are transmitted through the earlier years of life that are only subsequently developed. In like manner we often see qualities transmitted in a latent state through one or more generations, and then suddenly developed, as in the wonderful phenomena included under the term reversion. By virtue of these considerations it has been truly said that to know a man well we must know his relations—grandparents, parents, uncles, aunts, cousins, brothers, sisters, children—in them we shall often see developed his own latent tendencies. For this reason those who neglect collaterals in studying heredity are greatly in error.

It rarely happens that both parents are cancerous; but such an unfortunate combination undoubtedly increases the risk of morbid heredity.

Of 136 family histories of breast-cancer patients investigated by me in only 2 instances were *both* parents cancerous. These marriages produced 7 children, of whom 2 had died of cancer, or 1 in 3.5. Seven marriages, in which only *one* parent was cancerous, produced 62 children, of whom 10, or 1 in 6.2, had become cancerous. Six marriages in which, although neither parent was cancerous, the disease existed in their *collaterals*, produced 41 children, of whom 8, or 1 in 5.1, had become cancerous.

In spite of several sources of fallacy, I think this analysis gives fairly correct indications.

It will generally be found that the birth of the subjects of direct cancer heredity, dates from a period long anterior to that at which the disease appeared in their parents. Thus, in Broca's case, the four daughters of Madame Z., who all died cancerous, were born fifteen, twenty-five, twenty-six, and thirty years respectively before the period when their mother died of the disease—that which was latent in the parent was transmitted potentially to the offspring.

It frequently happens that such latent tendency to the disease in ancestors, although it never becomes effective in them, nevertheless does so in their descendants. Thus cases occur in which cancerous grandparents transmit the disease to their grandchildren, while their own offspring escape (*atavism*). This happened in 7 of the 136 cases of cancer of the female breast analysed by me, or in 5.1 per cent. In 3 of these cases the disease was inherited from the maternal grandmother, in 2 from the paternal grandmother, and in 2 from the paternal grandfather. In 3 cases the locality affected in the grandparents, as in the grandchildren, was the breast; in the other 4 cases the localisation of the disease in the grandparents differed from that in the grandchildren. Whether cancer is ever transmitted by reversion, after skipping more than a single generation—as often happens in physiological heredity—I am unable to state, and I know of no facts bearing on this point.

Much commoner than true atavism, or than heredity by direct descent from parents, is a form of inheritance in which the disease is transmitted through parents, etc., who themselves never manifest it, although their sisters, brothers, or other relatives do. On reference to my analysis of mammary-cancer cases, it will be seen that the inherited disease manifested itself in this way, in the father's sisters in ten families, the breast being the organ affected in five; and in six families in the mother's sisters, the breast being affected in four.

It will be gathered from the foregoing that what is transmitted in cancer heredity is not the disease itself, but a tendency or predisposition to the production of those conditions that may finally eventuate in it. It is a legitimate inference from what has been stated that the special tendency to cancer is of gradual evolution; and that without this antecedent preparation the disease can never be developed under ordinary circumstances.

Inherited cancer manifests itself much more frequently in the female than in the male relatives, although the disease is as often derived from the father's as from the mother's side of the family. My analyses show this very well. Thus of 47 affected relatives in the mammary-cancer series, there were 10 males to 37 females; and of 38 relatives in the uterine-cancer series, 8 were males and 30 females.

In cases of multiple family cancer this tendency of the inherited disease to repeat itself unduly in the female sex is especially noticeable. Thus, in Broca's case, all the persons attacked but one were females. Of the 19 daughters and granddaughters of Madame Z. who attained the age of thirty, 14 became cancerous; but out of 7 males only 1 was thus affected.

As in normal heredity—but with less constancy—cancer tends to appear in the offspring at about the same age that it appeared in the ancestor. Hence, like gout, cataract, phthisis, insanity, and some other heritable conditions, the disease usually does not manifest itself until an advanced period of post-embryonic life.

It has been suggested that during the course of its transmission by inheritance cancer may be *transmuted* into sarcoma or some form of non-malignant neoplasm. On *à priori* grounds, I have no objection to offer to this suggestion; but the facts collected by me show that the existence of such a coincidence in the family history of cancer patients is very exceptional. Of the one hundred and thirty-six family histories of women with breast cancer analysed by me, there were only two undoubted instances of non-malignant neoplasms in relatives; in one case the patient's mother, who was still alive and well, aged seventy-five, had a "tumor" removed from her thigh when she was fifty years old, which never recurred; in the other, the patient's father, who was still alive and well, had a lipoma of the back. Two other instances of so-called "tumor," one "internal" and the other "abdominal," were also reported, one in a patient's mother and the other in a mother's sister; but as both of these ended fatally, the disease was probably really malignant. This experience is by no means exceptional, for I have found equally few instances of non-malignant neoplasms in the ancestors of patients with cancer of other parts of the body, although I inquired just as carefully after the former as after the latter.

HEREDITARY PROCLIVITIES CORRELATED WITH CANCER.

The remarks I have to make on this subject are based upon the subjoined analyses of the family history of one hundred and thirty-four women with cancer of the breast, and of one hundred and twenty-nine uterine-cancer patients. These show:

1. That pulmonary *tubercle* is by far the most prevalent disease among the relatives of cancerous persons. Such a result is only what might have been expected *à priori*, considering the frequency of tuberculous disease in the community at large; but a great mistake has been made in taking it for granted, on this account, that the relatives of cancerous persons have no special proclivity to tubercle. On the contrary, as I shall proceed to show, such persons are very much more prone to it than the rest of the community; indeed, their liability to phthisis is so considerable, as even to equal that of the phthisical themselves.

No statistics show a greater amount of heredity in phthisis than Dr. R. Thompson's, because he has included in his list only those cases in which the family history had been very completely recorded. He obtained history of heredity in 44 per cent. of 5,000 consecutive phthisical cases—58 per cent. in females and 36 per cent. in males. Now, my analysis of the family history of 134 women with mammary cancer, shows a history of phthisis in 55 per cent., which is almost as high a proportion as Thompson's; similarly of 129 uterine-cancer patients, there was family history of phthisis in 60, or in 46.5 per cent. The amount of hereditary phthisis among the rest of the community is very much less than this; it has been estimated by Dovey, from analysis of the family history of 409 non-consumptive life policy-holders, at 10.8 per cent. Kuthy's analysis of the family history of 108 non-tuberculous persons gives a history of tubercle in 28.5 per cent., which is the highest estimate I know of. Nothing, therefore, can be plainer than that the relatives of cancerous patients, are very much more prone to tubercle than the rest of the community. This is borne out by the results deducible from my analysis of the causes of death of the brothers and sisters of patients with mammary cancer in 88 families. These averaged 8.8 members each, in all 774 individuals. Now, one or more deaths from phthisis took place in 40 of these families. Supposing only a single death to have occurred in each of them, this would be equivalent to 1 death from phthisis in 19 members, whereas the mortality from phthisis in the general population in 1885 amounted to 1 in 570. Similarly among 83 fathers of mammary-cancer patients who had died of various causes, the mortality from phthisis was 22, or 1 in 3.8; among 71 mothers it was 18, or 1 in 3.9, or among these 154 parents, it was 40, or 1 in 3.8; whereas the ratio of deaths from phthisis to the total mortality in the general community, in 1885, amounted only to 1 in 11. Analyses of the family history of other forms of cancer yield similar results.

Long study of the family history of cancer patients has convinced me that most of the latter are the *surviving members of tuberculous families;* and the facts just cited confirm this belief. Hence I conclude that no hereditary condition is more favorable to the development of cancer than that which gives proclivity to tubercle.

The much greater frequency with which obsolete tubercle is found in association with cancer than with most other diseases is also an argument in favor of this view. Thus, of 136 consecutive necropsies on women under my observation who died of cancer (uterus 79, breast 44, rectum 13), obsolete pulmonary tubercle was found in 17, or in 12.5 per cent;* whereas of 16,562 consecutive necropsies, tabulated by Heitler, on persons who had died of various causes—which included but 110 cases of cancer (0.6 per cent.)—obsolete tubercle was met with only in 789 cases, or in 4.7 per cent.†

Although cancer and tubercle are thus intimately connected, it is very rare to find both diseases in active progress in the same individual. I have met with this conjunction only twice in 136 cancer necropsies. Kelynack, at the Manchester Infirmary, found it only twice in 145 similar necropsies. From what has been stated, it is obvious that there is a certain antagonism between active tuberculous disease and cancer. The outbreak of cancer often follows or coincides with the healing of pulmonary tubercle, although in most cases the intervening period is fairly protracted. It is also evident that active tuberculous disease is of much less frequent occurrence in the cancerous than in the non-cancerous. There is, however, no absolute incompatibility between these morbid manifestations, but the comparative rarity of their coexistence is noteworthy. I even know of a few instances in which tuberculous disease and cancer of the same part have coexisted: thus Crawford has met with this conjunction in the mamma, Franqué in the uterus, Frerichs in the liver, Crone in the larynx, Dalton in the large intestine, Naegeli in the rectum, ileum, and cæcum; and Friedländer reports the development of cancer in the wall of a tuberculous cavity in the lung. Instances of "lupus cancer" have also been described.

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* Of 130 breast-cancer patients, 5 were aware of having had previous phthisical disease, or 3.8 per cent.

† The very conflicting data lately published as to the frequency of tuberculous lesions are not a little confusing and they evidently imply great diversity as to the criterion of obsolete tubercle. Thus Brouardel reports having found indications of cured pulmonary tubercle in 60 per cent. of all necropsies on persons over thirty who had died a violent death. Harris, at the Manchester Infirmary, found similar lesions in 39 per cent. of all necropsies on persons over twenty. Schlenker met with old tuberculous lesions in 44 per cent. of the bodies of those who had died of non-tuberculous diseases. Coats estimates the percentage at 25, Hughes Bennett at 20, and Fowler at 9. My own experience inclines me to accept Heitler's and Fowler's figures as being correct, when only well-marked lesions are taken into account; and this is the basis on which my data rest.

The combination of both phthisis and cancer in the same family's history was noted by me in 18 out of 134 mammary cases, or in 13.4 per cent.

Another consideration which accords with the foregoing is that, in families where cancer prevails, according to Moore, the elder members are more prone to become cancerous than the younger ones, the first-born being the most liable. Whereas, with regard to phthisis, it has been shown by Thompson that the younger members are the more liable—the greatest liability being with the last born.

For the following interesting account of the interrelations of cancer and phthisis during several generations, I am indebted to a medical gentleman, resident in the Isle of Wight. He says, in reference to the prevalence of these diseases there: "My mother's family is a typical island family; and I suppose I am related to every island family of two hundred years' standing. They were yeomen proprietors, farming their own land. In 1684 they owned a farm near Arreton, where they have lived ever since. My great-grandfather bought an adjoining farm at Standen; and my great-great-grandfather (and his father) owned an adjacent farm at Redway. Several of his children died of phthisis. Two of his daughters married my great-grandfather and his brother. Several of the brother's children died of phthisis. Redway passed to them by inheritance, and all the children were born there. One of my great-grandfather's sons died of cancer, and several of his grandsons; but none died of phthisis. In the next generation, however, several died of phthisis. None of the Redway family have since died of phthisis or cancer. Mine is the Standen family; and they have had cancer first and then phthisis. The Arreton family have had neither cancer nor phthisis. By the marriage of the two sisters with the two brothers, the same blood streams are responsible for the Redway, Standen, and Arreton families. The Arreton family are the longest-lived. The Standen branch is characterized by neurotic emotional temperament; and in the Redway branch there have been several dipsomaniacs. Both the men and women of all three families have been of a very affectionate disposition; for in two centuries no widow or widower ever married again. There has been no insanity in the family, who have always prided themselves on being married relations. The other old island families have a similar history; and in some cousins married. There are very few families, however, in which, besides cancer and phthisis, there have not been cases of insanity."

I have dwelt at some length on the interrelations of cancer and tubercle, because it appears to me to have an important bearing on the etiology and prophylaxis of cancer; and so far as I know, it has never before been set forth in its true light.

2. If similar investigations were set on foot with regard to other diseases, I believe it would be found that the tuberculous predisposition gives proclivity to many of them, as, for instance, it certainly does to *insanity*. Thus Clouston found tuberculous deposits twice as often in the bodies of those who died insane as in the bodies of those who died sane; and he has proved that hereditary predisposition to insanity is much greater among the tuberculous than among the non-tuberculous. In this connection it is worthy of note that the relatives of cancerous persons are more prone to insanity than are the relatives of the non-cancerous; at least this is the conclusion I draw from the fact that 51 female cancer patients under my observation gave a family history of insanity in 7 cases, or in 13.7 per cent.; whereas 29 women with non-malignant neoplasms knew of insane relatives in only 3 instances, or in 10.4 per cent.; and the latter is probably a higher percentage than would be met within the general community.

The liability of insane persons to cancer is decidedly below the average; and idiots seem to be even less susceptible. Thus of 5,373 adult lunatics who died while under treatment at the Hanwell and Hitchen Asylums (1870–91) only 125 died of cancer, or 1 in 39; of 2,741 women, 101 died cancerous, or 1 in 27, and of 2,623 men 34, or 1 in 77.

3. Many authors regard *apoplexy* as a manifestation of the same disposition, of which insanity is also an outcome; and my analysis shows that this disease is unduly prevalent among the relatives of cancerous persons. Thus of 154 parents of women with mammary cancer who died of various causes, 17 died of apoplexy, or 1 in 9; whereas the ratio of deaths from apoplexy to the total mortality of the general population in 1884, was only 1 in 36. Similar undue frequency of this disease is noticeable among the brothers and sisters of these cancer patients; for, while 1 in 258 of the latter died of apoplexy, the mortality from it in the general community amounted, in 1884, to only 1 in 1,841.

4. There is reason to believe that the members of cancer families

are also unduly prone to *arthritic manifestations*, as was the case, for instance, in the Bonaparte family, Prince Pierre having died of heart disease consequent on rheumatic fever, and Napoleon III. of stone in the bladder. My analysis shows 12 deaths from heart disease among 154 parents of breast-cancer patients, or 1 in 12.8; whereas in the general community the corresponding ratio in 1884, was 1 to 79. From rheumatic fever my analysis shows 1 death in 154 parents; whereas the rate for the community at large, in 1884, was 1 in 195. Of 160 cases analysed by Nunn, gout and rheumatism were traced in 15.

There is also evidence of a considerable amount of heart disease and rheumatic fever among the patient's brothers and sisters; and of 130 breast-cancer patients under my observation, 11 had previously suffered from rheumatic fever and 6 from rheumatism.

5. There still remain to be considered two other proclivities to which the members of cancer families are remarkably subject, viz., longevity and great reproductive fecundity.

The evidence furnished by my analysis as to the *longevity* of the parents of cancer patients is of the most striking and conclusive kind. To prove this it will suffice to mention only a few of the leading facts derived from the mammary-cancer analysis.

Of 112 dead fathers 14 attained the age of 80, which is equivalent to 1,250 per 10,000, whereas in the general population only 463 males live to this age out of 10,000.

Of 103 dead mothers 17 attained the age of 80, which is equivalent to 1,650 per 10,000, whereas in the general population only 682 females live to this age out of 10,000.

Of these 215 dead parents 2 attained the age of 95, which is equivalent to 93 per 10,000, whereas in the general population only 21 per 10,000 live to this age.

At first sight this result appears to be in contradiction with the conclusion previously arrived at, that the relatives of cancer patients are especially liable to pulmonary tubercle; but it must be borne in mind that these cancer families are generally exceedingly numerous. Striking confirmatory evidence is furnished by inquiring into the family history of centenarians and aged persons, whence it appears that a large proportion of these—twenty per cent. in the case of females—are the surviving members of phthisical families. It is evident, therefore, that the constitutional peculiarity which is associated with tubercle is by no means incompatible with longevity.

6. Equally conclusive is the evidence as to the great *fecundity* of cancer families. Thus, 110 of these mammary-cancer families averaged 8.8 members in each family, or 968 members in all; whereas,

according to Farr, in the general community the average number to a family is 4.6, so that an equal number of families would include only 506 members.

Inasmuch as a tendency to twinning usually goes with excessive fertility, it is probable that an undue proportion of twins is met with in these cancer families, although I have not specially investigated this point.

The foregoing conclusions, although based upon facts derived from the study of the family history of women with cancer of the breast and uterus, are nevertheless, as I have specially ascertained, equally valid for cancer of all other parts of the body.

Analysis of the Family History of 134 Women with Cancer of the Breast:

The Fathers.—Of 129 cases in which inquiries were made with regard to the fathers, in 117 they were *dead*, and in 12 still *alive*. The *causes of death* were known in 83 cases, as follows: phthisis in 22 cases; heart disease, 11; apoplexy, 9; bronchitis, 8; cancer, 5; dropsy, 5; old age, 4; accident, 3; cholera, 2; strangulated hernia, 2; renal disease, diabetes, fever, diarrhœa, white swelling of knee, sunstroke, erysipelas, typhoid fever, ulcer of leg (hemorrhage), suicide (alcoholism), insanity and cerebral softening, each 1 case.

Of those who had died of *phthisis*, in 7 cases other members of the family had also died of this disease. Twelve of these fathers who had died of causes other than phthisis were, however, of phthisical families. Thus of these 83 fathers, 34 (40.9 per cent.) were of phthisical families.

There were among them 5 deaths from *cancer* (6 per cent.); the localities affected being the breast, lip, hand, liver, and "internal." Seven fathers who had died of causes other than cancer were, however, of cancerous families:

The relatives thus affected and the seats of the disease were as follows: (1) Father died, aged 57, of heart disease; his father died, aged 60, of cancer of the œsophagus; and his mother's first cousin died of cancer of the œsophagus. (2) Father died, aged 55, of phthisis; his mother died of cancer of the breast. (3) Father died, aged 69, insane; his sister died of cancer of the breast. (4) Father died, aged 64, of apoplexy; his father died, aged 76, of cancer of the nose. (5) Father died, aged 80, of apoplexy; his sister died, aged 75, of cancer of the scalp. (6) Father died, aged 62, of apoplexy; his sister died of internal cancer. (7) Father died, aged 73, of heart disease; his mother died of cancer of the breast. Thus of these 83 fathers, 12 (14.4 per cent.) were of cancerous families.

The average *age of the fathers at death*, in 112 cases, was 62.4

years; the oldest 96 (14 having attained or exceeded 80 years), the youngest 30.

Of the 12 *fathers still alive,* 2 were subject to heart disease and dropsy, and 1 to chronic rheumatism, 1 to chronic bronchitis, and 1 had a lipoma of the back. The others were in good health.

The average *age* (in the 9 cases in which it is stated) was 72.4 years; the oldest 83 (2 attained or exceeded 80), the youngest 60. Two of these 12 fathers were of *phthisical* families, each having lost a sister from this disease, as well as from cancer. Four of them were of *cancerous* families, the relatives affected and the seats of the disease being as follows: (1) Sister died, aged 40, of cancer of the mouth, and another sister died, at about the same age, of cancer of the face. (2—4) In 2 cases a sister died of cancer of the breast; and in 1 case a sister was suffering from cancer of the breast.

The Mothers.—Of 125 cases in which inquiries were made with regard to the mothers, in 105 they were dead, and in 20 still alive. The causes of death were known in 71 cases, as follows: phthisis, 18 cases; apoplexy, 8; dropsy, 8; cancer, 7; bronchitis, 6; liver disease, 3; pneumonia, 3; cholera, 3; childbed, 2; old age, 2. Abdominal tumor, chest disease, rheumatic fever, diabetes, jaundice, peritonitis, quinsy, typhoid fever, heart disease, strangulated hernia, and sudden death in bed, each 1 case.

Of those who had died of phthisis, in 3 cases other members of their families had also died of this disease. Six of these mothers, who had died of causes other than phthisis, were, however, of phthisical families. Thus, of these 71 mothers 24 (33.9 per cent.) were of phthisical families.

There were among them 7 deaths from cancer (9.8 per cent.), the localities affected being the uterus (2), internal (2), breast, stomach, and tongue, each 1. Six of these mothers who had died of causes other than cancer were, however, of cancerous families. The relatives thus affected, and the seats of the disease were as follows: (1) Mother died, aged 70, of phthisis; a relative of hers died of cancer of breast. (2) Mother died, aged 82, suddenly in bed; her sister died of cancer of breast. (3) Mother died, aged 68, of apoplexy; her sister died of cancer of tongue. (4) Mother died, aged 70, of apoplexy; her cousin died of cancer—locality not stated. (5) Mother died, aged 66, of bronchitis; her mother died of cancer of uterus. (6) Mother died of phthisis; her sister died of cancer of breast. Thus, of these 71 mothers, 13 (18.3 per cent.) were of cancerous families. The average age of the mothers at death, in 103 cases, was 62 years; the oldest within a few months of 100 (17 having attained or exceeded 80 years), the youngest 25.

Of the 20 mothers still alive, all save 2 (bronchitis 1, and spinal disease 1) were well. Their average age (in 16 cases) amounted to 71.5 years; the oldest 84 (3 had attained or exceeded 80), the youngest 60. Of these 20 mothers 5 were of phthisical and 2 of cancerous families.

Cansanguinity in the Parents.—As to this, inquiries were made in 33 cases, with the result that in 2 instances the parents were blood relations. In 1 case they were first coüsins; the father died of heart disease, aged 66, and his father died insane; the mother died, aged 78, of dropsy. There were 5 children of the marriage; 2 died in infancy, and 2 sisters were still alive and well. There was no history of cancer, tumor, or phthisis in either family.

In the other case the parents were third or fourth cousins. The father died, aged 55, of phthisis, and his mother died of cancer of the breast. The mother died, aged 80, of old age.

The Patients' Brothers and Sisters.—In 88 families the following causes of death were noted among the adults: Phthisis (one or more deaths) in 40 families; heart disease, 8; dropsy, 6; cancer, 5; childbed, 5; rheumatic fever, 3; apoplexy, 3; bronchitis, 3; typhoid fever, 3; traumatism, 3; fever, 2; smallpox, 2; cholera, 2; peritonitis, 2; and hepatic disease, 2 families. Cerebral disease, scarlet fever, yellow fever, insanity, delirium tremens, tuberculous abscesses, pleurisy, diabetes, pneumonia, tuberculosis of the bowels, pyæmia, jaundice, tuberculous arthritis, and strangulated hernia, each 1 case.

Of the families in which *phthisis* prevailed, in 15 more than a single member had died of this disease.

Of 110 families, the *number of members in each family* was noted, with the result that the smallest family consisted of 1 (two instances), the largest of 19 (two of 17), the average of 8.8.

The Occurrence of Phthisis.—Of 134 families, among the adults, one or more relatives had died of or were subjects to phthisis in 74, or 55.2 per cent. In 37 of these families more than a single individual had died of this disease.

The relatives thus affected may be conveniently arranged as follows:

Both paternal grandparents in	1	family.
Paternal grandmother	1	"
Both parents	5	families.
Fathers	16	"
Father's brothers and sisters	18	"
Mothers	13	"
Mother's brothers and sisters	8	"
Patient's brothers and sisters	37	"

The Combination of Phthisis and Cancer.—Of 134 cases, in 18 there was history of both phthisis and cancer in the same family. Thus:

Phthisis on	Father's side in 9 families.
	Mother's side in 1 family.
	Patient's brothers and sisters in 4 families.
Cancer on	Father's side in 2 families.
	Mother's side in 12 families.
	Patient's brothers and sisters in 2 families.
Cancer and Phthisis on	Father's side in 3 families.
	Mother's side in 3 families.

The Occurrence of Insanity.—As to this, inquiries were made in 18 families: in 3 there was history of insanity, the patient's paternal grandfather, father, and sister being the relatives respectively affected.

Analysis of the Family History of 129 Cases of Cancer of the Uterus:

The Fathers.—Of 126 cases in which inquiries were made, in 102 the fathers were *dead*, and in 24 *alive*. The *causes of death* were known in 70 cases, as follows: Phthisis in 24 cases; accident or violent death in 7; bronchitis, 7; apoplexy, 6; heart disease, 4; dropsy, 4; insanity, 3; typhoid fever, 2; fever, 2; cholera, 2; pleurisy, lung disease, epilepsy, gout, sunstroke, hæmoptysis, pneumonia, rheumatic fever, and delirium tremens, of each 1 case.

Of those who died of *phthisis*, in 11 cases other members of their families had also died of this disease. Four of these fathers, who had died of causes other than phthisis, were, however, of phthisical families. Thus, of these 70 fathers, 28 (40 per cent.) were of phthisical families.

There was not a single death from *cancer* among the fathers. Two of them (2.8 per cent.) were, however, of cancerous families, one of them having lost a brother of cancer of the stomach, and 3 cousins—1 female of cancer of the breast, and 2 males of the neck and foot respectively.

The average age *at death*, in 97 cases, was 57 years—the youngest, 26; the oldest, 95 (5 others having attained or exceeded 80 years).

Of the 24 fathers *still alive*, 23 were well and 1 was insane. Their average age (in 20 cases) was 72.4 years—the youngest, 60; the oldest, 85 years (3 others having attained or exceeded the age of 80).

The Mothers.—Of 124 cases, in 95 the mothers were *dead*, and in 29 *alive*.

The *causes of death* were known in 66 cases, as follows: Phthisis in 14; cancer, 8; bronchitis, 8; apoplexy, 7; heart disease, 5; childbed 3; pleurisy, 3; dropsy, 2; diarrhœa, 2; fever, 2; old age, 2; strangulated hernia, 2; epilepsy, abdominal tumor, cholera, accident, syncope (from fright), peritonitis, rheumatic fever, and jaundice, of each 1 case.

Of those who died of *phthisis*, in 8 cases other members of their families had also died of this disease. Six of the mothers, who had died of causes other than phthisis, were, however, of phthisical families. Thus of these 66 mothers, 20 (30.3 per cent.) were of phthisical families.

Eight of the mothers died of *cancer* (2 of the uterus, 2 of the breast, 2 of the stomach, 1 of the intestine, and 1 of the face). Six of these mothers, who had died of causes other than cancer, were, however, of cancerous families, the relations thus affected and the seats of the disease being as follows: Mother's sister in 4 cases (breast, 2; uterus, 1; locality not stated, 1); 1 mother's sister and 2 female cousins in 1 case (internal in all); female cousin on mother's side in 1 case (abdominal). Thus of these 66 mothers, 14 (21.2 per cent.) were of cancerous families.

Their average *age at death* (in 90 cases) was 60 years, the youngest 25, the oldest 99 (7 others having attained or exceeded the age of 80).

Of the 29 mothers *still alive*, 25 were in good health and 4 were ill (apoplexy, 2; heart disease, 1; and bronchitis, 1). Their average age (in 27 cases), 68.8 years—the youngest, 54; the oldest, 90 (one other having attained the age of 80).

Consanguinity in the Parents.—As to this, inquiries were made in 50 cases, with the result that in only one instance were the parents blood relations. In this case they were first cousins: both parents were still alive and well—the father aged 75, the mother aged 70. They had ten children, and there was no history of cancer, phthisis, or insanity in either family.

The Patients' Brothers and Sisters.—In 81 families the following *causes of death* were noted among the adults: phthisis (one or more deaths) in 41 families; dropsy in 6; cancer in 5; heart disease, 5; insanity, 3; typhoid fever, 3; spinal disease, 2; morbus coxæ, 2; scarlet fever, 2; tumor of cheek (aged 16), smallpox, cholera, lymphadenosis, bronchitis, pleurisy, cerebral disease, apoplexy, accident, peritonitis, and ulcer of leg, of each 1 case.

Of the families in which *phthisis* prevailed, more than a single member had died of the disease in 20.

One of the patients had a sister alive, suffering from *cancer* of the uterus.

The *number of members in each family* (in 117 cases) averaged 7; the smallest family consisted of 1 (of which there were 4 instances), the largest of 21. One of the patients was one of four at a birth, the rest of the family consisting of three pairs of twins.

The Occurrence of Phthisis.—Of 129 families, one or more relatives had died of or were subject to phthisis in 60, or 46.5 per cent. In 36 of these families more than a single member had suffered from this disease. The relatives thus affected may be shown as follows:

Father's father	in 1 family.
Fathers	" 20 families.
Father's brothers and sisters	" 16 "
Both parents	" 3 "
Mother's father	" 1 family.
Mothers	" 12 families.
Mother's brothers and sisters	" 7 "
Patient's brothers and sisters (one or more).	" 42 "

The Combination of Phthisis and Cancer.—Of 129 families there was history of *both phthisis and cancer* in the same family in 14. Thus:

Phthisis	Father's side	in 7 families.
	Mother's "	" 1 family.
	Patient's brothers and sisters	" 4 families.
Cancer	Father's side	" 1 family.
	Mother's "	" 6 families.
Cancer and Phthisis.	Father's side	" 2 families.
	Mother's "	" 3 "
	Patient's sister (cancer) and brother (phthisis)	" 1 family.

The Occurrence of Insanity.—Inquiries were made as to this in 25 cases, with the result that there was history of insanity in 3 families, in 2 cases the patients' fathers being affected, and in 1 case the patient's brother.

The General Health of Cancer Patients.

Long-continued observation of cancer patients, in the early stage of the disease, has convinced me that most of those affected are large, robust, well-nourished, florid persons, who appear to be overflowing with health and vitality; and they often present a considerable amount of *embonpoint.* Mr. and Mrs. John Bull, as so frequently depicted in the pages of *Punch,* are the physical types of the majority of cancer patients. Such types are indicative of general hypernutrition.

At first there seems to be some difficulty in reconciling this appearance of rude health, with the conclusion previously arrived at, that most cancer patients are the surviving members of tuberculous families; but in reality there is here no contradiction, for it commonly happens that the surviving members of such families are remarkable for their robust and vigorous constitutions. The famous Astley

Cooper was a striking example of this; yet he was of a very tuberculous family, having lost five near relatives of this disease; moreover, in his youth he had hæmoptysis, which was rightly supposed to be due to pulmonary tubercle, for when in accordance with his last instructions his body was submitted to post-mortem examination, a healed tuberculous lesion was found at the apex of his lung. According to my views he was a very likely subject for cancer, and although he escaped, it would be interesting to know whether his descendants have been equally fortunate.

Beneke describes cancer patients as having large hearts and wide arteries, with small lungs, large livers, and long, large, capacious intestines. This quite accords with what I have myself observed, that cancer patients usually are of a coarse physical type. Those recently attacked never present a cachectic appearance. The small, pale, ill-nourished, and overworked women, of the type so familiar in Lancashire and other large industrial centres, are seldom the victims of this disease.

I have previously referred to many facts which indicate that the causation of cancer is intimately associated with the conditions of nutrition; and it is especially such influences as are comprised under the terms *alimentation* and *domestication* that seem to me to be of paramount importance.

In the present imperfect state of our knowledge, it is singularly difficult to determine the precise effect of diet in this direction in any particular case; because in all probability its influence becomes appreciable only very slowly, or after more than a single generation of individuals has been exposed to it. Hence the failure of the praiseworthy attempt of the British Medical Association's Collective Investigation Committee to solve this problem. From returns collected by this committee, it appears that of 194 cancer patients, 123 had been moderate eaters, 59 small eaters, and 12 large eaters. With regard to meat, 99 had been moderate, 78 small, and 16 large eaters. There was not a single strict vegetarian among them, and only a few had been great eaters of vegetables.

That cancer is less prevalent in vegetarian than in flesh-eating communities is generally believed, and the following considerations are favorable to this belief:

In Ireland, where a large proportion of the population live chiefly on vegetable diet, the prevalence of cancer, as I have previously pointed out, is much less than in either of the sister countries.

Beneke's statistics show that cancer is rare in prisons, where but little animal food is allowed and hard work is exacted. The experience of those engaged in workhouses, lunatic asylums, and similar institutions, where very little meat is allowed, is of like import. The comparative rarity of the disease among the intemperate is also noteworthy in this connection, for persons of drunken and dissolute habits are seldom affected.

The remarkable fact that in New Zealand and New South Wales men are more liable to cancer than women is probably due, as MacDonald believes, to their gluttonous habits in respect to meat eating. "Meat for breakfast, lunch, dinner, tea, and supper, just like the porridge pot * in Scotland."

The greater prevalence of cancer in rural than in urban districts, and, in the latter, its greater incidence in those localities where the well-to-do and easy-going reside, rather than among the poor and working classes, point to the same conclusion. It is, however, certain that vegetarians are not completely exempt.

The alleged immunity of savages, and the great prevalence of the disease in all civilised communities, is probably largely attributable to the influence of diet. At any rate, it is certain that savages are, as a rule, less well fed than are the members of modern communities.

Leblanc and others believe that carnivorous animals are more prone to develop malignant disease than herbivora.

Meat-eating communities are, as a rule, also *alcohol*-consuming. There is, however, no evidence to show that the habitual consumption of alcoholic liquors *per se* in any way predisposes to cancer. The British Medical Association's inquiry indicates that the effect of this habit has rather the opposite tendency; and this coincides with the results of my own observations, which show that cancer patients have almost invariably led regular, sober, and industrious lives. The victims of chronic alcoholism are generally dyspeptic and ill-nourished, and they often manifest a remarkable aversion to meat.

In the course of my investigations into the life history of cancer patients, I have been much struck with the extreme rarity of *syphilis* in such persons.

Of 165 female breast-cancer patients, specially examined by me, not a single one presented undoubted signs of having had syphilis. Of 160 uterine-cancer patients, similarly examined, only one presented signs of having had syphilis.

From the foregoing and from other indications of like import, it may be inferred that the victims of constitutional syphilis are much less prone to cancer than the non-syphilitic. This comparative immunity of the syphilitic, is probably due to the depraved nutrition and lowered vitality, caused by the contamination of the system with the syphilitic virus. Turenne was probably aware of this, when he syphilised his recently operated cancer patients, with the object of preventing recurrence.

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* Much less common in these latter days of increasing affluence.

Here it may be mentioned that cancerous diseases are met with in the animal world, where syphilis is unknown, so that syphilis cannot be regarded as a cause of cancer, as some have alleged.

In connection with this subject, reference may be made to the impunity of these female cancer patients from *chronic ulcer of the leg*, of which there was not a single instance in my patients. Considering the commonness of the latter affection in women over middle age, this immunity of the cancer patients is certainly highly remarkable. In the eighteenth century it was customary to establish "issues" on each of the four limbs, after operations for the removal of cancer, with the object of preventing recurrence "by opening a passage for the cancerous virus"; and, under the influence of similar ideas, the operation wounds were prevented from closing by first intention. It is probable that such methods do exert some deterrent influence on the disease, acting like the syphilitic virus—but less powerfully—by lowering the general vitality.

I have seen it stated that the subjects of *osteitis deformans* are specially prone to malignant disease; with regard to this, I have to point out that of over 1,000 cases of malignant disease investigated by me—of which I now have written records—not a single one was complicated by this disease: 170 cases of breast cancer in women and 160 uterine-cancer cases are included in this list.

It has been urged by Lambotte and others that erysipelatous and suppurative affections are of comparatively rare occurrence in the cancerous; and the inference has been drawn that these maladies—by vaccinal action—protect from cancer.

In order to test the value of the alleged rarity of *erysipelas* in the cancerous—which is at variance with the impression I had formed after an extensive experience of cancer—I have examined the statistical data of some of the large London hospitals, with the following results: Of 395 extirpations of the breast for cancer, 40 were subsequently attacked by erysipelas, or 10 per cent.; whereas of 173 scalp wounds, under treatment at one of these hospitals during the same period, only 8 were attacked by erysipelas, or 4.6 per cent.

It would thus appear—as my own experience suggested—that, instead of being immune from erysipelas, the cancerous are more than twice as prone to it as the non-cancerous.

Lambotte also states that there is seldom any evidence of suppurative affections in the pathological antecedents of the cancerous. As I was at some pains, several years ago, to determine the maladies to which the cancerous are prone, I find that I have at hand the requisite data for testing the validity of this statement. Thus of 130 uterine-cancer patients under my observation, 9 had previously suffered from smallpox, 5 from phthisis, 2 from erysipelas, 2 from abscess, 2 from fistula in ano, and 1 each from necrosis, lupus, and furunculosis. Of 130 breast-cancer patients, 5 had previously suffered from phthisis, 4 from smallpox, 4 from ulceration of the uterus, 3 from erysipelas, 3 from old abscesses of the neck, and 1 each from fistulo in ano, suppurative tuberculous disease of the knee-joint, otorrhœa, and whitlow. Thus of these 260 female cancer patients, 46, or 18 per cent., had previously suffered from some form of suppurative disease.

To compare with the foregoing, I have found that of 75 women with non-cancerous tumors, 12 had suffered from previous suppurative diseases, or 16 per cent., as follows: phthisis, 3; abscess, 4; erysipelas, 2; and 1 each from smallpox, ulcer of the uterus, and hip-joint disease. From this it appears that Lambotte's second proposition is as unreliable as his first; for, as these data show, the cancerous are just as prone to suppurative disease as the non-cancerous.

I have seen a great many cancer patients attacked by erysipelatous and suppurative affections; but I have never noticed consequent amelioration of the disease, much less anything approaching a cure. In many such cases these superinduced affections lead to a rapidly fatal issue. I believe that most of the alleged cures of cancerous disease by erysipelas inoculations, etc., are attributable to diagnostic errors; at any rate I am convinced that tuberculous, syphilitic, and chronic inflammatory affections, especially in the breast and uterus, are often mistaken for malignant disease by experienced surgeons; and I suspect that cases of actinomycosis, mycosis fungoides, etc., are more frequently mistaken for malignant disease than is generally believed. Consequently every new specific for cancer has no difficulty in justifying itself by a crop of "cures," although I am convinced that cancer has never really been cured by any external application or internal medicament whatsoever.

As for those exceptional cases of malignant disease, in which—after an attack of erysipelas or after inoculation with its toxins, etc. —arrest or diminution has been observed, I believe such conditions are not due to any specific or vaccinal action of the remedy, for similar effects have been produced by many widely different conditions. For instance, many examples of the regression of mammary cancer in connection with acute outbreaks of pulmonary tubercle have been reported. Perrion has seen the same disease subside, after an operation for goitre, followed by much suppuration. Téallier has often noticed retardation in the progress of uterine cancer during lactation. An instance of the regression of mammary sarcoma, after artificially induced delivery, has been reported by Jahr. In cases of intra-abdominal malignant disease, Bidwell and others have seen marked amelioration ensue after simple exploratory laparotomy. Beatson's cases of regression of mammary cancer after oöphorectomy evidently belong to this category. Similar results have ensued after tuberculin injections, etc. Many other such instances might be cited. In the penultimate stages of most exhaustive illnesses, malignant growths often become stationary, and even appear to wither and dry up shortly before death.

The only feature common to all such cases is the extremely debilitated condition to which the patients are reduced, and I think there can be no doubt that enfeebled vitality is the cause of such improvement as is noticeable. The condition of the patient is, in fact, similar to that brought about by what is known as the starvation treatment of cancer, as formerly practised with some success by Hufeland and others.

The liability of insane persons and idiots to cancer, as I have elsewhere indicated, is also decidedly below the average; and they are generally debilitated and of low vitality. The like is true of prison and workhouse inmates.

The alleged immunity of the cancerous from infectious diseases, as signalised by Labarsch, is not corroborated by such data as I have collected. Thus of my 267 female cancer patients, 13 had suffered from smallpox (4.8 per cent.), 16 from typhoid fever (6 per cent.), and 1.1 per cent. from pneumonia; whereas of 83 women with non-cancerous tumors, 1.2 per cent. had suffered from smallpox, 6 per cent. from typhoid fever, and 2 per cent. from pneumonia.

With regard to rheumatic fever, of my 267 female cancer patients 24, or 8.9 per cent., had suffered from it; whereas of 83 women with non-cancerous tumors, 7 had been thus affected, or 8.4 per cent.

Virchow believes that the cancerous are more prone to inflammatory affections than the non-cancerous.

I have often noticed on the face, chest, and upper limbs of breast-cancer patients minute pink telangeiectases; but these are also commonly seen on the non-cancerous of corresponding age. The small outgrowths of warty or dermoid structures, said by De Morgan to coincide with or follow the development of cancer, I have rarely seen in association with breast and uterine cancer; nor have I noticed that eczema, psoriasis, or other dermatoses often appear in the course of this disease, as Bazin and Hardy allege. Herpetic manifestations I have rather more frequently seen. Charcot mentions having often noticed "Heberden's nodes" in the subjects of uterine and mammary cancer.

Some authors attach great importance to grief, anxiety, and mental distress as causes of cancer, and they have adduced statistics in support of their belief. With regard to this, I can only say that the majority of cancer patients, whose life history I have investigated, appeared to me to have been less exposed to depressing influences of this kind, than most women of corresponding age in the general population.

In most modern text-books on gynecology, reference is made to the alleged greater prevalence of cancer among the poor and ill-nourished than among those more fortunately circumstanced. This doctrine has lately received its apotheosis at the hands of Sinclair, of Manchester, who says: "My experience is that uterine cancer occurs only among the working classes; the apparent exceptions are so few that they are hardly worth discussing. . . . So marked is the difference of incidence that it might be reasonably affirmed, that if we could place all the lower orders, who suffer from privation and depressing environment, for a generation or two in the position of the more favored, we should stamp out cancer."

In support of such statements, reference is made to Hofmeier's statistics, which show that of 16,800 patients at the Berlin Polyclinic, 3.6 per cent. suffered from cancer; whereas in Schroeder's private clinic of 9,400 patients, only 2.18 per cent. were similarly affected.

Such data cannot fairly be quoted as evidence of the greater prevalence of cancer among the poor than the rich, although they may raise a presumption of this kind.

Against the acceptance of this doctrine, I would urge the following considerations, most of which I have previously had occasion to mention.

1. During the last half-century the wealth of the country has more than doubled; its pauperism has diminished more than one-half; crime has declined; sanitary conditions have greatly improved; the mortality from zymotic, tuberculous, and many other diseases has markedly diminished; wages have gone up, while the prices of most commodities have fallen to an extraordinary extent;* the consumption of meat per head has more than doubled, having now (1897) reached the

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* The recently issued report of the Royal Commission on Agriculture (1897) shows: (1) That during the last quarter of a century there has been a fall of over 40 per cent. in the price of staple cereals, which in the case of wheat is 50 per cent. (2) That in beef the fall has been from 24 to 40 per cent.; in mutton from 20 to 30 per cent. (3) In dairy product the price has declined 30 per cent. (4) In potatoes 20 to 30 per cent., etc.

amazing total of one hundred and thirty-one pounds per head per year. The bulk of the people are better paid, better housed, and better fed than ever they have been before—in short, just such conditions have prevailed as Dr. Sinclair alleges are necessary to stamp out cancer; but, instead of having decreased during this period, the cancer mortality has more than quadrupled, the uterus participating in due proportion. The only part of the United Kingdom where the cancer mortality has undergone no such marked increase is Ireland, which is just the one part where material progress has been deficient.

2. The registrar-general's reports show that the cancer mortality is lowest where the struggle for existence is hardest, where the conditions of life are most squalid, the density of population greatest, the tubercle mortality highest, the general mortality highest, and where sanitation is least perfect—in short, among the industrial classes in our great towns; whereas, among the wealthy and well-to-do and among the agricultural community, there the cancer mortality is highest. The experience of those engaged in prisons, workhouses, and lunatic asylums points in the same direction; for cancer is comparatively rare among the inmates of such institutions, as it is also among the intemperate. Of like import is the great frequency of the disease in civilised communities, whereas among savages it is almost unknown. Moreover, in the animal world, it is only the domesticated that are affected; in a state of nature these diseases are unknown.

3. The *ensemble* of facts relative to the life history of cancer patients shows, that they have almost invariably led regular, sober, and industrious lives. Persons of drunken and dissolute habits are comparatively seldom affected. Of 325 female cancer patients under my observation, not a single one had ever been addicted to prostitution—so far as I could ascertain—and, what is still more remarkable, only a single one presented undoubted signs of having had syphilis. The marked fecundity of these cancer patients, and the rarity of sterility and abortion among them, all point in the same direction; for sterility and abortion are of frequent occurrence in prostitutes and in the syphilitic.

Such considerations as the foregoing seem to me to negative the doctrine of cancer being *morbus miseriæ.* They point to the greater prevalence of the disease among the well-to-do and easy-going, who habitually eat more than is good for them.

In conclusion, I must here express entire concurrence with Moore's statement "that cancer is eminently a disease of persons whose previous life has been healthy, and whose nutritive vigor gives them otherwise a prospect of long life."

It is remarkable how little the *general nutrition* of cancer patients often appears to suffer—in the absence of ulceration—even when the disease has lasted for a considerable time.

Thus of 75 consecutive mammary cases, when they first came under my observation, 4 were markedly cachectic or sallow (primary 3, recurrent 1), 8 were emaciated (primary 6, recurrent 2), and 14 pale (primary 10, recurrent 4); the remaining 57 (primary 47, recurrent 10) were well nourished and healthy looking, 7 of them being obese.

The following analysis of the *occupations* usually followed by the 300 female cancer patients of my list affords indirect evidence in favor of the foregoing views. Thus, of 144 mammary-cancer patients:

Of 80, *married*—housewifes, 66; governesses, 2; laundresses, 2; nurses, 2; and 1 each employed in a straw-hat factory, at needlework, in a boot factory, as cook, mantlemaker, tailor, servant, charwoman.

Of 20, *widowed*—housework, 8; laundry, 3; cooks, 2; monthly nurses, 2; and 1 each: dressmaker, employee in a paper factory, employee in a factory, midwife, lady's maid.

Of 44, *single*—cooks, 9; servants, 9; dressmakers, 5; at home, 4; governesses, 2; school teachers, 2; and 1 each as follows: staymaker, nurse, lady's companion, monthly nurse, upholstress.

Of 156 uterine-cancer patients:—Of 106 *married*—housewifes, 68; charwomen, 8; laundresses, 7; tailoresses, 5; needlework, 5; monthly nurses, 4; cooks, 2; servants, 2; actress, employee in paper factory, nurse, straw-hat maker, and shop assistant, of each 1.

Of 40 *widowed*—independent means, 8; housekeepers, 5; laundresses, 4; charwomen, 4; needlework, 3; nurses, 3; cooks, 2; shop assistants, 2; dressmakers, 2; obstetric nurses, 2; lady's maid, bath attendant, flowermaker, straw-hat maker, school mistress, of each 1.

Of 10 *single*—servants, 2; lodging-house keeper, barmaid, waitress, cook, no occupation, tailoress, needleworker, shop assistant, of each 1.

Although it cannot be said that persons of any rank or station in society are exempt from cancer, there are nevertheless some remarkable differences in the incidence of the disease among the various social strata. I have already had occasion to point out the greater prevalence of the disease among the well-to-do and among the agricultural community, than among the industrial classes in our great towns, as well as its comparative rarity among paupers, lunatics, and the prison population.

This subject was specially investigated in the tenth United States census report, and the results arrived at are in general agreement with my conclusions. It is there shown that agriculturalists, hotel and restaurant keepers, the professional classes, carpenters, and sailors are very much more prone to cancer than iron and steel workers, miners, clerks, printers, cotton, silk, and wool operatives, railway-men, etc.

For these various classes the cancer death rates per 100,000 living were as follows: Agriculturalists, 59.8; hotel and restaurant keepers, 52.7; carpenters and joiners, 48.2; physicians, 47.8; clergymen, 46.3; sailors, 44.5, etc.; miners and colliers, 14.5; iron and steel workers, 12.2; cotton, silk, and wool operatives, 9.9; clerks, salesmen, etc., 8.3; railway-men, 7.9; and printers, 6.8.

In England chimneysweeps are said to be more prone to cancer than any other workers; and among colliers and miners the disease is relatively infrequent. Workers in tar, paraffin, arsenic, etc., are specially prone to certain forms of cutaneous cancer. There are good reasons for believing that farm laborers, gardeners, sailors, and those who follow other out-of-door occupations, are unduly prone to cancer of the lower lip.

Of 36 men with cancer of the lower lip who came under my observation in London, 5 were farm laborers, 5 general laborers, 3 sailors, 2 bricklayers, and 1 each as follows: saddler, cowman, blacksmith, stoker, worker in a paper-factory, piano-maker, sewerman, bailiff, gardener, brazier, carpenter, gas-fitter, costermonger, carman, commercial agent, boatman, waiter, soldier, fireman, and groom.

The large proportion of patients engaged in out-of-door occupations in this list is very remarkable, especially when regard is had to the sedentary occupations followed by the great bulk of the London population, whence these cases were drawn.

In certain cobalt and nickel mines those employed have been observed to be prone to malignant pulmonary diseases.

Some idea of the *non-cancerous morbid conditions* to which women with cancer of the *breast* are liable, may be gathered from the subjoined analytical statements.

1. In 165 consecutive patients the following associated lesions, etc., were noticed at the time they *came under observation:* Arcus senilis in 5, pains in the limbs (chiefly thighs) in 4, scanty growth of hair on the face in 3, old corneal leucomata in 2, lipoma in 2, molluscum fibrosum (large and pendulous) in 2, scars of old abscesses of neck, etc., in 2, varicoid capillaries of cheeks in 2, extreme deafness in 2, spontaneous fracture of femur in 2, and each in one case—whitlow, lobular hypertrophy of opposite breast and scars of old abscesses, general tuberculous enlargement of lymphatic glands and scars of old abscesses, old ankylosis of knee after suppurative white swelling, jaundice, nausea and vomiting, bronchitis, pneumonia, erythema, pasty swollen face from renal disease, chronic alcoholism, bronzed complexion, freckled complexion, smallpox pitted, internal

strabismus, enlarged thyroid, enlarged lymph glands of submaxillary region, cataract and posterior synechiæ.

2. Of 130 breast-cancer patients, whose *previous health* was investigated, 100 stated that it had been habitually good (with no serious illness since youth in 52), 19 that it had been indifferent, and 11 that it had been bad.

The following *previous diseases* were noted as having occurred among these patients since childhood: Bronchitis in 17 cases, rheumatic fever in 11, typhoid fever in 11, chronic rheumatism in 6, phthisis in 5, ulcer of the uterus in 4, smallpox in 4, erysipelas in 4, dyspepsia in 3, alcoholism in 3, scarlet fever in 3, hemorrhoids in 2, migraine in 2, varicose veins in the legs in 2, peritonitis in 2, and each in 1 case—extreme myopia, glaucoma, iritis, neuralgia, disorganized eyeball, corneal ulcers, femoral hernia, enlarged cervical glands, quinsy, fistulo in ano, suppurative white swelling of the knee, measles, otorrhœa, ulcerated sore throat, heart disease, laryngitis, cholera, phlegmasia dolens, small fibroadenoma of breast (thirty-five years' duration), jaundice and gall-stones, diphtheria, cystitis, nervous debility, intermittent fever, syncopal attacks, hypertrophied tonsils.

3. *Post-mortem examination* of the bodies of 44 women,* the subjects of breast cancer, revealed the presence of the following non-cancerous lesions, etc.: The general condition of the body was noted in 40 cases. It was emaciated in 18; well nourished, 11 (obese, 5), of these, 8 (obese, 2) had died shortly after operation; moderately nourished, 7 (of these 2 had died shortly after operation); sallow, 2; icteric, 2; bronzed and mottled, 1.

Lungs.—Old pleural adhesions in 24 cases (general in 16—both lungs in 13, one lung in 3; in 8 cases adhesions confined to one or both upper lobes); emphysema in 12; acute pleurisy with effusion in 11 (6 of these of septic origin, 4 due to invasion of the thorax by direct extension of the primary disease, and 1 secondary to tuberculous pneumonia); collapse of lung in 7 (in 5 cases secondary to acute pleural effusion and in 2 to invasion of the thorax by cancer); congestion in 6; phthisis in 6 (the phthisical lesions in 4 cases were in the form of old scarring and pigmentation at each apex associated with old pleural adhesions, and in 1 of these cases with a cavity and in another with caseous old nodules as well; in the other 2 cases the disease was in active progress; in 1 there was a large cavity surrounded by tuberculous consolidation, and in the other almost the whole of both lungs was consolidated by caseous tubercle, with cavities and softening in places); bronchitis in 5; hydrothorax in 3; each in 1 case—recent pleural adhesions, old dried-up empyema with partial collapse, hypostatic pneumonia. In not a single instance were both lungs normal.

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* In 5 of these 44 cases death was due to intercurrent affections, not directly connected with the cancerous disease; in 10 cases death had supervened shortly after operation.

Heart.—Small and atrophied in 5 cases; atheroma of aortic arch in 5; atheroma and thickening of mitral valve in 4; atheroma and thickening of tricuspid valve, etc., in 3; atheroma of aortic valves in 2; large aneurysm of aortic arch in 2; walls of heart soft and flabby in 2; milk-white patch on anterior surface of the ventricles in 2; acute pericarditis (septic, 1; secondary to invasion by cancer, 1) in 2; and each in 1 case—mitral stenosis, atheroma of the pulmonary valves and aorta, general hypertrophy, excess of fat on the surface, deeply stained endocardium. In 25 cases the heart was normal.

Liver.—Fatty in 17 cases; gall-stones in 7 (or in 16 per cent. of these 44 cancer necropsies);* nutmeg, 3; cirrhosis, 3; congestion, 3; small, 2; cloudy swelling, 1; and multiple angioma in 1 case. In only a single case was the liver normal.

Spleen.—Large and congested in 5, very small in 2, and normal in 35 cases.

Kidneys.—Chronic interstitial nephritis (small and granular kidneys) in 16 cases; fatty in 5; renal calculi (uric acid, 2; phosphatic, 1) in 3; congestion, 2; acute pyelitis (associated with acute cystitis) in 1 case; cloudy swelling in 1; very small in 1 case. In 18 cases the kidneys were normal.

Gastrointestinal Tract.—Acute peritonitis in 2 cases (1 due to perforation, 1 to secondary cancer); gastric catarrh in 1 case; femoral omental hernia in 1; ascites in 1; fistula between gall-bladder and duodenum (owing to blocking of the common bile duct by a cancerous growth in the head of the pancreas) in 1 case. In 38 cases the gastrointestinal tract was normal.

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* With regard to the relative frequency of gall-stones in the cancerous, of 281 cancer necropsies analysed by me (in which no hepatic or gastric cancers are included), gall-stones were present in 18, or in 6.4 per cent.; 181 were women, with gall-stones in 14, or in 7.7 per cent.; and 100 were men, with gall-stones in 4 cases. Of 103 necropsies for malignant disease at St. George's Hospital, analysed by Muir, gall-stones were present in 13, or in 12.6 per cent.; of 67 men in 7.9 per cent., and of 40 women, in 20 per cent.

Of 777 non-cancerous necropsies—mostly on adults—at the Manchester Infirmary, Brockbank found gall-stones in 34, or in 4.4 per cent.; of 228 necropsies on females they were met with in 18, or in 7.9 per cent.; and of 542 necropsies on males in 16, or in 2.9 per cent. It would thus appear that the cancerous, like the tuberculous and the insane, are more prone to gall-stones than the generality of the population of corresponding age and sex, although in a less degree. Of 44 female breast-cancer necropsies there were gall-stones in 7, or in 16 per cent.; of 79 uterine-cancer necropsies gall-stones were present in 5, or in 6.3 per cent.; and in 52 necropsies for cancer of the tongue and mouth in males gall-stones were met with in but a single case.

Other Lesions.—Uterine fibromyomata in 5 cases; soft polypi of the uterus in 3 cases; and each in 1 case—dermoid cyst of the ovary, small parovarian cysts, small multilocular ovarian cystomata, pyometria and pyosalpinx (owing to occlusion of the os uteri), old ununited fracture of the neck of the femur, spontaneous fracture of both femora (part of general fragilitas ossium unassociated with secondary growth), cold abscess in the axilla (on the side opposite to the cancerous breast).

In 144 uterine-cancer patients the following non-cancerous morbid conditions were noted when the patients first came under observation:

1. Dementia in 4 cases, bronchitis in 2, arcus senilis in 2, deafness (extreme) in 2, capillaries of the cheeks unduly obvious in 2; and each in 1 case—lupus, freckles, prolapsed uterus, xanthelasma palpebrarum, patellar exostosis, and smallpox scars.

2. In 137 cases the *previous health* had been good in 104 (with no serious illness since youth in 70), indifferent in 21, and bad in 12.

The following *previous diseases* were noted as having recurred since childhood: Rheumatic fever in 13 cases, typhoid fever in 9, smallpox in 9, bronchitis in 8, leucorrhœa in 7, dyspepsia in 5, hæmoptysis in 4, pleurisy in 4, migraine in 4, pneumonia in 3, inflammation of the uterus in 3, prolapse of the uterus in 3, hemorrhoids in 3, chronic rheumatism in 3, hemiplegia in 2, peritonitis in 2, erysipelas in 2, psoriasis in 2, fistula in ano in 2, and each in 1 case—epilepsy, palpitation, abscess of the neck, abscess of the breast, jaundice, lupus, necrosis, enlarged glands in the neck, arthritis of the knee, cholera, and boils.

3. *Post-mortem examination* of the bodies of 79 uterine-cancer patients revealed the following non-cancerous lesions, etc.: In 68 cases the *general condition of the body* was noted; it was emaciated in 60, moderately nourished in 6, well nourished in 2; sallowness was noted in 5 cases and purpura in 1 case.

Lungs.—Old pleural adhesions in 41 cases (general, 22—both lungs in 20, the right alone in 2; in 16 cases adhesions confined to the region of the apex—both 10, left 4, right 2); emphysema in 23; obsolete tubercle in 12 (both apices in 9 cases, right alone in 2, left in 1—all these lesions were associated with old pleural adhesions); bronchitis in 7; hypostatic pneumonia in 2; hydrothorax in 2; and each in 1 case—bronchopneumonia, abscess at the apex, acute pleuropneumonia, and acute pleurisy. In 15 cases the lungs were normal.

Heart.—Small in 9 cases, old mitral disease in 9, atheroma of the aortic arch in 6, old disease of the aortic valves in 4, hypertrophy of the ventricles (right in 2, left in 1, both in 1), dilatation of the right side in 3, old disease of the auriculoventricular valves in 3, old pericardial adhesions in 2, acute pericarditis in 2, brown atrophy in 2, fatty degeneration in 2, mitral vegetations (recent) 1, milk-white patch on the anterior surface of the right ventricle 1. In 44 cases the heart was normal.

Liver.—Fatty in 21 cases, nutmeg in 7, gall-stones in 5, small and brown in 2, amyloid in 2; and each in 1 case, old syphilitic scarring, congestion, thick opaque capsule, and cirrhosis. In 40 cases the liver was normal.

Spleen.—Small in 8 cases, amyloid in 4, large in 2, pale in 2. In 63 cases the spleen was normal.

Peritoneum.—Pelvic contents matted together by old adhesions in 34 cases,* old abdominal peritoneal adhesions in 10 cases, acute general peritonitis in 8 cases, ascites in 1 case, effusion of chyle in 1 case.

Urinary Organs.—Double hydronephrosis with atrophy in 52 cases; single hydronephrosis with atrophy in 7 cases (in 5 the opposite kidney was healthy, in 3 diseased); double pyonephrosis in 3 cases; single pyonephrosis (with the opposite kidney diseased in all) in 3 cases; hydronephrosis of one side with pyonephrosis of the other in 2 cases; double chronic interstitial nephritis in 3 cases; acute nephritis of one kidney with chronic nephritis of the other in 1 case; 1 case each as follows—renal cysts (large), cystic adrenals, deposit of urates. If 15 cases there was acute cystitis. In every case there was extensive renal disease.

Other Lesions.—Uterine fibromyomata in 5 cases, double pyosalpinx in 4, pyometria in 3, small aneurysms at the base of the brain in 2, single hydrosalpinx in 2; and each in 1 case—single pyosalpinx, ulcer of the rectum, scar of the old gastric ulcer, and cerebral hemorrhage.

The Prevalence of Cancer and Its Increase.

In the course of organic evolution, some types of disease—like species—have diminished and become extinct, while others have increased and become more prevalent. In comparatively recent times, plague, typhus fever, leprosy, ague, and dysentery have almost or quite disappeared from this country; smallpox and other zymotic diseases have greatly diminished; while phthisis and other tuberculous disease are now decidedly on the wane. On the other hand, cancer —a disease known to have existed in its present form from the most remote times of which we have any record—has steadily increased during the last half-century, and is still increasing, and this in spite of diminution in the general death rate. Among the few other morbid conditions that show any increase, insanity and suicide are the chief.

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* Causing *intestinal obstruction* in 3 cases, as follows: (1) There were two exceeding small constrictions of the gut, one at the ileum—six inches above the ileocæcal valve—and the other at the sigmoid flexure of the colon; both due to adhesions of the gut to the diseased uterus. (2) The body of the tuterus was enormously enlarged and infiltrated with cancer, compressing the rectum against the sacrum. (3) At the brim of the pelvis the sigmoid flexure of the colon was constricted, twisted, and adherent to the left ovary, which was cancerous. In this case the rectum also was compressed—to a certain extent—by the uterine growth which had invaded its anterior wall.

Prior to 1837, when the registration act came into operation, we have no reliable information as to the prevalence of cancer.

In 1840 it caused 2,786 deaths, the proportion being 1 in 5,646 of the total population, 1 in 129 of the total mortality, or 177 per million living.

In 1896 the deaths due to it numbered 23,521, being 1 in 1,306 of the total population, 1 in 22 of total mortality, or 764 per million living.

Thus the proportionate mortality from cancer is now more than four times greater than it was half a century ago. Among women of thirty-five years of age and upwards, it has increased from 1 in 91 for the decennial period, 1851–60, to 1 in 12 for the period 1887–89. From the extent of the mortality and the average duration of the disease,* I calculate that there cannot be fewer than 45,000 persons now suffering from cancer in England and Wales; whereas, in 1840, the number was only about 5,500.

In this respect its position is unique, for no other disease can show anything like such an immense increase. It seems certain that if unchecked cancer will ere long become one of the commonest diseases of modern communities.

In illustration of this subject I have compiled the following table, which shows the increase in England and Wales since 1840:

TABLE SHOWING THE PREVALENCE OF CANCER AND ITS INCREASE IN ENGLAND AND WALES.

Year.	Total population.	Total deaths.	Cancer deaths.	Cancer death rate per million living.	Proportion to population.	Proportion to total deaths.
1840	15,730.813	359,687	2,786	177	1 to 5,646	1 to 129
1850	17,773,324	368,995	4,966	279	1 " 3,579	1 " 74
1855	18,829,000	426,646	6,016	319	1 " 3,129	1 " 70
1860	19,902,713	422,721	6,827	343	1 " 2,915	1 " 62
1865	21,145,151	490,909	7,922	372	1 " 2,670	1 " 62
1870	22,501,316	515,329	9,530	424	1 " 2,361	1 " 54
1875	24,045,385	546,453	11,336	471	1 " 2,121	1 " 48

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* Taken at the low estimate of two years.

TABLE SHOWING THE PREVALENCE OF CANCER AND ITS INCREASE IN ENGLAND AND WALES.—*Continued.*

Year.	Total Population.	Total deaths.	Cancer Deaths.	Cancer death rate per million living.	Proportion to population.	Proportion to total deaths.
1880	25,714,288	528,624	13,210	502	1 " 1,946	1 " 40
1881	25,974,439	491,937	13,542	520	1 " 1,918	1 " 36
1882	26,413,861	516,654	14,057	532	1 " 1,879	1 " 36
1883	26,770,744	522,997	14,614	546	1 " 1,763	1 " 35
1884	27,132,449	530,828	15,192	559	1 " 1,786	1 " 35
1885	27,499,041	522,750	15,560	566	1 " 1,767	1 " 33
1886	27,870,586	537,276	16,243	583	1 " 1,715	1 " 33
1887	28,247,151	530,758	17,113	606	1 " 1,650	1 " 31
1888	28,628,804	510,971	17,506	610	1 " 1,635	1 " 29
1889*	29,015,613	518,353	18,654	643	1 " 1,555	1 " 27
1890†	28,762,287	562,248	19,433	676	1 " 1,480	1 " 28
1891	29,081,047	587,925	20,117	692	1 " 1,445	1 " 29
1892	29,405,054	559,684	20,353	690	1 " 1,445	1 " 27
1893	29,731,100	569,958	21,135	711	1 " 1,407	1 " 27
1894	30,060,763	498,827	21,422	713	1 " 1,403	1 " 23
1895	30,383,047	568,997	22,945	755	1 " 1,324	1 " 24
1896	30,717,355	526,727	23,521	764	1 " 1,306	1 " 22

* Estimated on the 1881 census. † Estimated on the 1891 census.

Mere increase of population will not account for this continuously progressive augmentation of the cancer death rate, as is evident from the fact that its rate of increase has proportionally been much in excess of this; and there is far too much uniformity in the variations of the increments of increase in the long succession of years, to warrant its being ascribed to improved diagnosis or other casual error. Moreover, the increase has not been confined to one or a few parts of the body; but it has involved them all—on the whole without any considerable disturbance of the normal proportionate localisation ratios.

Again, as I have previously indicated, the increase has been diffused over the whole country, instead of being limited to certain areas only; so that those parts that formerly had the highest, lowest, and average cancer death rates still preserve their distinction in these respects, although the cancer mortality has everywhere augmented. There can, therefore, be no doubt as to its reality.

The attempt to explain the increasing cancer mortality as due to the average age of the population having advanced, and the consequent liability of greater numbers, will not bear critical examination; for the saving of life in modern times has been mainly confined to early years. The death rates of males over thirty-five, and of females over forty-five, have remained stationary or actually increased; while the numbers that attain old age have decreased. This heavy mortality at post-meridian ages is no doubt largely due to the survival in augmented numbers of weakly lives, artificially prolonged by improved conditions of existence; but not more than a small fraction of the increased cancer mortality can be thus accounted for. Besides, as I have previously mentioned, it is a mistake to assume that increased cancer mortality is a necessary corollary of the survival of augmented numbers to the cancer age.

The returns for Scotland exhibit a similar increase, as is shown by the following figures:

	Cancer death rate per million living.
1861 to 65	404
1866 " 70	428
1871 " 75	468
1876 " 80	504
1881 " 85	540
1890	610
1892	670

In most civilised countries, where statistical records have been kept, somewhat similar increases have been observed.

The following table shows the increase in the United States* during the decennium 1880–90:

Year.	Total population.	Total deaths.	Cancer deaths.	Proportion to population.	Proportion to total deaths.	Cancer death rate per million living.
1880	50,155,783	756,893	14,849	1 in 3,310	1 to 51	296
1890	62,622,250	875,521	20,984	1 " 2,984	1 " 41	319

In Australasia cancer is also increasing in prevalence.

The New South Wales cancer mortality in 1885 was 2.67 per 10,000 living; in 1890 it had increased to 3.92, and in 1894 to 5.16. Mullins gives the following table in illustration of this subject:

Years.	TOTAL CANCER DEATHS.		CANCER DEATH RATE PER 1,000,000 LIVING.	
	Males.	Females.	Males.	Females.
1870–74	415	289	289	242
1875–79	505	371	293	259
1880–84	632	486	287	268
1885–89	950	798	348	353
1890–93	1,045	862	416	405

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*Among the blacks of the United States malignant disease is reported to have been comparatively rare prior to the abolition of slavery; but since then the liability to it has been steadily increasing, so that among modern negroes it is fairly common.

In Victoria the cancer mortality in 1871–80 was 3.71 per 10,000 living; in 1882–86 it was 4.7; and in 1891, 5.5.

In New Zealand the increase was from 3.26 in 1877–88 to 4.4 in 1891. According to Fell, the number of deaths from cancer in 1897 was more than double what it had been five years previously, although the population had increased by less than one-third.

There has also been some increase of the disease in Tasmania and in South Australia.

In the Netherlands the increase was from 4.9 per 10,000 living in 1867–79 to 6.5 in 1884–88; in Prussia from 3.1 in 1881 to 3.8 in 1887; and in Italy from 4.2 in 1887 to 4.9 in 1896.

In Norway the cancer deaths increased from 32 per 1,000 of the total mortality in 1877 to 60 per 1,000 in 1886–87.

In the chief cities the disease has likewise increased.

The London cancer death rates—per million living—for the last three decennia are as follows:

	Persons.	Males.	Females.
1861–70	487	285	664
1871–80	554	352	732
1881–90	683	504	843

The Paris cancer mortality increased from 1 in 30 of the total deaths in 1875 to 1 in 24 in 1889 and to 1 in 19 in 1894. In 1865 the Paris cancer mortality was 8.4 per 10,000 living; in 1870, 9.1; in 1880, 9.4; in 1885, 9.8; and in 1890, 10.8, at which figure it still stood in 1897. Dr. J. Bertillon kindly supplied me with these data.

The New York cancer mortality increased from 520 per million living in 1885 to 628 in 1890; that of Philadelphia from 440 in 1872–76 to 558 in 1890, etc.

In all the above instances the augmented cancer mortality has coincided with progressive population, increased national wealth, diminished pauperism, and marked improvement in the general well-being. It seems to me impossible to regard these coincidences otherwise than as the result of cause and effect.

It accords with this view that in Ireland—where less favorable conditions have prevailed—the cancer death rate has been much lower than in either of the sister countries; and for many years it has shown no such marked increase as in the latter, as is shown by the subjoined figures:

	Per million living.
1873	330
1874	330
1877	350
1878	360
1879	340
1880	340

Year.	Total population.	Total deaths.	Cancer deaths.	Cancer death rate per million living.	Proportion to population.	Proportion to total deaths.
1885	4,924,342	90,712	1,925	391	1 in 2,558	1 to 47
1886	4,889,498	87,292	2,029	415	1 " 2,409	1 " 43
1887	4,837,313	88,585	2,067	427	1 " 2,340	1 " 42
1888	4,777,534	85,892	2,003	419	1 " 2,358	1 " 42
1889	4,730,566	82,908	2,134	451	1 " 2,212	1 " 38
1890	4,688,462	85,850	2,145	458	1 " 2,185	1 " 40
1891	4,681,248	85,999	2,163	462	1 " 2,164	1 " 39
1892	4,638,169	90,044	2,221	479	1 " 2,088	1 " 40
1893	4,615,312	82,821	2,280	494	1 " 2,024	1 " 36

A remarkable fact about the increasing cancer mortality of Great Britain is that it has affected males to a much greater extent than females.

In the decennium 1871–80 the increase for males was 62 per cent., whereas for females it only amounted to 43 per cent.; in the succeeding decennium, 1881–90, the increase for males was 78 per cent., as compared with 42 per cent. for females. In further illustration of the subject I have compiled the following table:

TABLE SHOWING THE RELATIVE INCREASE OF CANCER AMONG MALES AND FEMALES.

Period.	Male cancer death rate.	Female cancer death rate.	Sex ratio.
1851–60	195	434	1 to 2.2
1861–70	244	523	1 " 2.1
1871–80	315	622	1 " 1.9
1881–91	430	739	1 " 1.7
1891–95	547	868	1 " 1.6
1896	618	901	1 " 1.4

In 1896 the male cancer death rate was 618 per million living, whereas that for females was 901, the sex ratio being 1 male to 1.4 females: 1 male died of cancer for every 29 male deaths, and 1 female for every 17 female deaths.

Thus while the cancer mortality among males since 1861–70 has increased 153 per cent., the increase among females has been only 74 per cent. It seems to me probable that this undue incidence of the increasing cancer mortality on males may be ascribed to the fact that of late, as the result of urbanisation, the conditions of life for men have come to resemble more closely those for women than heretofore. Excess of food, with want of proper exercise and changed surroundings, are, I think, its chief causative agents.

It is worthy of note that, for both sexes, the percentage of cancer deaths above fifty-five is greater than it used to be; and a larger proportion of the male deaths occurs after sixty-five than of the female deaths.

The state of affairs I have just set forth, is of such grave import that every civilised nation ought at once to institute special investigations, for the purpose of determining the best means of combating the disease.

In this connection attention should be given to the remarkable decline in the death rate from phthisis and other tuberculous diseases, that has coincided with the great increase in the cancer mortality; for while the latter has more than quadrupled during the last fifty years, the former has diminished by more than one-half. The latest ascertained cancer death rate is the highest on record, while that from tubercle is the lowest. The subject is further illustrated by the following data:

TABLE SHOWING THE DECENNIAL MORTALITY PER MILLION LIVING FROM CANCER, PHTHISIS, AND OTHER TUBERCULOUS DISEASES.

	1861-70.	1871-80.	1881-90.
Cancer	384	468	589
Phthisis	2,475	2,116	1,724
Other tuberculous diseases.	765	747	696

This tendency is still in full force, for in 1896 the death rate from pulmonary tubercle was only 1,307 per million, the lowest ever recorded; whereas the cancer mortality for the same year was the highest ever recorded (764 per million). I regard this decline in the prevalence of tuberculous disease as the outcome of improved hygienic conditions, due to that augmented prosperity which, I have endeavored to show, by its action in another direction is also responsible for the increased cancer mortality.

It seems to me exceedingly probable, from considerations derived from the study of the family history of cancer patients, that a large proportion of those thus saved from tubercle, eventually perish of cancer and insanity; and I think the increase in the latter diseases has largely been brought about in this way.

What are the determining causes of these extraordinary occurrences? Considering the complexity of the subject and the imperfection of our knowledge, categorical answers to such questions can hardly be expected. Nevertheless, I need not be deterred, on this account, from formulating such explanatory conceptions as, after careful study of the subject, seem likely to be useful.

At the outset I may as well state my conviction as to the improbability of the increase being directly ascribable to any single causative factor.

It is generally agreed, that the stability of the equilibration of the constituent elements of living bodies, is more profoundly affected by sudden and violent changes in the environment, than by any other group of circumstances. The invariable tendency of such changes is to render the organisms that survive them more plastic; that is to say, more prone to deviate from the normal routine of growth and development. The natural history of cancer shows that it is a disease belonging to this category. In this connection the great proclivity to cancer shown by immigrants into the United States and Australia —to which I have previously called attention—is of interest.

The last half century has witnessed the transition of millions of people from the agricultural to the industrial mode of life; this stupendous vicissitude, suddenly precipitated, undoubtedly constitutes one of the most profound and far-reaching environmental changes that the human race has ever experienced. I believe that the increase of cancer has sprung out of impulses thus determined.

One of the most potent and widespread effects of the conditions of life incidental to industrialism, on the health of those involved in its influence, is its tendency to induce certain degenerative changes which render those affected incapable of properly resisting tuberculous and other morbid excitations. It will probably be found that these changes ultimately depend upon defective cellular metabolism; and I believe this is the common root whence spring such diverse morbid manifestations as tubercle, cancer, and insanity.

In times of great prosperity—such as those with which we are here concerned—the evil effects of industrial conditions of life are, to a certain extent, mitigated by sanitation, good feeding, etc. Thus many of those who have acquired morbid predisposition, nevertheless escape destruction. It would, however, be a great mistake, on this account, to regard such persons as being normally constituted; their degeneracy is none the less real because it is not obviously manifest. According to my belief, it is from these persons and their descendants that the ranks of the great cancer army are being constantly recruited.

This view of the question throws an interesting sidelight on the curious paradox that a high cancer mortality is an indication of good sanitation—in which there certainly is some truth.

Probably no single factor is more potent in determining the outbreak of cancer in the predisposed than high feeding. There can be no doubt that the greed for food, manifested by modern communities, is altogether out of proportion to their present requirements. Many indications point to the gluttonous consumption of meat, which is such a characteristic feature of the age, as likely to be specially harmful in this respect.

Statistics show that the consumption of meat has for many years been increasing by leaps and bounds, and it has now, as I have before stated, reached the total of one hundred and thirty-one pounds per head per year, which is more than double what it was half a century ago, when the conditions of life were more compatible with high feeding.*

When excessive quantities of such highly stimulating forms of nutriment are ingested by persons whose cellular metabolism is defective, it seems probable that there may thus be excited, in those parts of the body where vital processes are still active, such excessive and disorderly cellular proliferation as may eventuate in cancer.

No doubt other factors coöperate, and among these I should be especially inclined to name deficient exercise and probably also deficiency in fresh vegetable food.

Such influences as are comprised under the terms of alimentation and domestication seem to me to be of paramount importance in the etiology of cancer.

It follows from the foregoing that the tendency to cancer may be increased by unsuitable modes of living, and *vice versa*. Hence, as I have elsewhere pointed out ("Diseases of the Breast," London, 1894), if we wish to mitigate the prevalence of this disease, we must first of all seek out those environmental conditions that favor its development; and by avoiding these we shall then be able to effect our object. It well may be that we shall even eventually succeed, in this way, in completely suppressing the disease. This desirable consummation is far from being so hopeless and remote as is usually believed. Pathologists should therefore concentrate their attention on this aspect of the subject, and I am convinced that their exertions will not be in vain. I have already indicated some of the chief lines along which such investigations should proceed. In my opinion, it is only by progress thus directed that the cure of cancer is ever likely to be effected.

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*In the middle ages a man was considered to be in easy circumstances who could procure fresh meat for his dinner once a week. In many British workhouses, to this day, the meat allowance is not much in excess of this. Herbivora are said to be unusually prone to tubercle: and carnivora to be comparatively but little subject to it. It has been maintained, when meat forms too small a proportion of the diet of human beings, that tubercle is apt to supervene.

PATHOLOGICAL ANATOMY.

The Biological Distribution of Cancer and Other Neoplasms.

Considering the great advances lately made in most branches of biology, the comparative stagnation of pathology is a surprising and regrettable anomaly; and I suppose no part of pathology is in a more backward and neglected condition than that which comprises comparative pathology. Notwithstanding their excellent opportunities, veterinarians have hitherto contributed very little to the advancement of the science of the diseases of animals.

Morphological and physiological processes being similar in the animal world and in mankind, it is only reasonable to suppose that pathological processes will also manifest a certain similarity. From what is known of the diseases of animals, this supposition appears to be fully justified; at any rate, so far as tumors are concerned, it has been ascertained that the analogy holds good. Hence in studying the etiology of malignant and other neoplasms, it is important to recollect that they are not peculiar to mankind, nor even to animals; for it seems probable that such growths may arise, under certain conditions, in any multicellular animal or vegetable being.

In a state of nature these abnormalities hardly ever occur. It is exclusively among domesticated varieties, or those that have been kept long in confinement, that they are met with. Even under such circumstances, malignant epithelial neoplasms are of rare occurrence in the animal world, as compared with mankind; however, cases have been met with in most of our domesticated animals, especially in dogs, horses, pigs, and cats, and in tame rats and mice. The mammary glands of many female animals are liable to be thus affected.

The following examples have lately been recorded: a large cancerous tumor of the mammary gland of a mare, containing cartilaginous and osseous structures, by Scott; a large cancerous cystic tumor of the mamma of a bitch, by Batt; a multilocular cystic tumor, with intracystic growths, from the mamma of a bitch, by Sibley; cancer of the mamma of a cat, by Spencer; squamous epithelioma of the penis of a horse, by Patteson; cancer of the testis of an Italian greyhound (Museum of the Royal College of Surgeons); malignant melanoma of a horse, with widespread dissemination, by Hutchinson; cancer of the prostate of a dog, by De Rouville; columnar epithelioma of the lung of a dog, by Silcock; cancer of the pituitary body of an anubis baboon, by Goodhart.

Much commoner and more widely diffused are the sarcomata, which have been met with in nearly all classes of animals, from fish upwards; but they oftenest occur among the ordinary domesticated animals, *e.g.*, dog, horse, cat, cow, sheep, common fowl, etc. Male dogs, horses, asses, and pigs are particularly liable to sarcoma of the testis. Horses are also subject to psammomata of the brain, of which Saundby has described an example. Another form of tumor to which horses—especially those of white or gray color—are prone, is melanoma—the region of the anus or root of the tail being the part usually affected. Other situations in which melanotic growths have been observed in these animals are the vulva, scapular region, skin, axilla, and lungs. In the Hunterian Museum there is a specimen of melanoma of a white cow's udder (No. 469, Pathological Series). Most of these melanotic growths in horses are of a chronic nature, and comparatively benign; but occasionally they manifest all the properties of malignancy, with widespread dissemination.

According to Rayer, carnivorous animals are more prone to malignant disease than herbivorous ones; whereas, with regard to tubercle, the relative liability is just the converse. In this connection it is noteworthy that monkeys manifest very little tendency to neoplasms, malignant or otherwise; whereas of domestic animals dogs are far more frequently affected than any others.

Of 39 malignant tumors in dogs, tabulated by Cadiot and Roger, the mammary gland was the seat of the disease in 18—11 were cancers and 7 sarcomas (3 chondroid and 2 osteoid); in 3 cases the testis was affected, and in 3 the bones of the face. Of 5 malignant tumors in horses the seat of the disease were the mamma (2), the testis, the face, and the stomach.

The following instances of sarcoma have lately been reported: in the lower jaw of a horse, by Lediard; in the upper jaw of a horse, by Pike; retroperitoneal lymphosarcoma of a dog, by Spencer; peritracheal sarcoma of a dog, by Spencer; sarcoma of the palate of an otter hound, by Lediard; intraabdominal lymphosarcoma of a marsupial, by Eve; spindle-celled sarcoma of the head of a dog, by Creighton; alveolar sarcoma of the thoracic region of a plover; a large cystic myxoma attached to the colon of a sheep, by Sharp; melanotic sarcoma of the forefoot of a dog (Museum of the Royal College of Surgeons).

Fibromas, enchondromas, and osteomas are as common and as widely diffused as sarcomas.

Cooper has lately described a case of fibroma of a cow's udder; and Shattock, fibroadenoma of the mammary rudiment of a male pied rat.

Mammary fibroadenoma of female dogs, cats, etc., is fairly common; and enchondromatous mammary growths are much oftener met with in these animals than in mankind.

Adams and Langlois have recently reported examples of mammary enchondromata and osteomata in bitches; and, as pointed out by Virchow, growths of this kind are often associated with malignant disease.

Fatty tumors are occasionally seen in domesticated animals, such as the ox, horse, sheep, and fowl.

A. J. Williams has described a large retroperitoneal lipoma of a terrier dog.

Cysts occur frequently in most domesticated animals, their commonest situation being in the ovaries; Slater has met with an ovarian tumor in a pheasant. An example of teratoma of the sphenoid region in a calf has been described by Windle.

I am not aware that any true neoplasm has hitherto been demonstrated in any invertebrate animal; but the pathology of the invertebrata and of the lower vertebrata is practically *terra incognita.*

That vegetable organisms, such as trees, are liable to be affected by malignant and non-malignant neoplasms, I have shown in my work on the "Principles of Cancer and Tumor Formation," London, 1888.

The Initial Seats of Neoplasms and Their Relative Frequency.

In this section I propose briefly to set forth some of the results of a statistical investigation as to the initial seats of neoplasms; and then to make passing reference to the bearing of the facts thus revealed, on certain aspects of the question of histogenesis.

An analysis of 13,824 primary neoplasms of all parts, in patients of both sexes, consecutively under treatment at four large London hospitals, yields the following results:

TABLE I.—A. SHOWING RELATIVE FREQUENCY OF THE NEOPLASTIC PROCESS IN ITS CHIEF SEATS IN BOTH SEXES (BASED ON 13,824 CASES).

	Per cent.
Uterus	19.2
Mammæ	17 5
Skin	9.4
Connective tissue (general)	7.7
Tongue and mouth	6.3
Ovary	5.8
External genitalia	5.1
Bones (*ex.* maxillæ)	4.0
Rectum	3.3
Maxillæ	2.9
Stomach	2.6
Lower lip	2.6
All other localities	13 6
	100.0

B. Showing the Relative Frequency of the Neoplastic Process in its Chief Seats in Males (Based on 4,957 Cases).

	Per cent.
Skin	16.4
Tongue and mouth	15.9
Connective tissue (general)	9.4
Lips	7.3
External genitalia	6.1
Bones (*ex.* maxillæ)	6.1
Rectum	5.0
Stomach	4.8
Maxillæ	3.9
Brain	3.4
Œsophagus	3.1
Testes	2.0
Mammæ	0.5
Prostate	0.2
All other localities	15.9
	100.0

C. Showing the Relative Frequency of the Neoplastic Process in its Chief Seats in Females (Based on 9,227 Cases).

	Per cent.
Uterus	28.7
Mammæ	26.0
Ovaries	8.7
Connective tissue (general)	6.9
Skin	5.9
External genitalia	4.6
Bones (*ex.* maxillæ)	2.9
Rectum	2.5
Maxillæ	2.4
Tongue and mouth	1.6
Brain	1.4
Stomach	1.2
Liver	1.2
All other localities	5.8
	100.0

A noteworthy feature in connection with these analyses is the great frequency with which, in females, the reproductive organs—uterus, mammæ, ovaries, etc.—are attacked; in fact, nearly seventy per cent. of all neoplasms in women arise from these organs.

The very great frequency with which the uterus and mammæ are affected is particularly striking. From the fact that both of these parts are subject to remarkable postembryonic developmental changes, it may be inferred that they are normally rich in cells which still retain much of their embryonic capabilities for growth and development. It is probably owing to this peculiarity that they are so much more prone to originate neoplasms than other parts of the body.

In favor of this view it may be urged of neoplasms in general that they arise from archiblastic (epithelial) structures much more frequently than they do from parablastic (connective tissue) ones. Thus, of these 13,824 primary neoplasms, 72 per cent. originated from the archiblast, and only 28 per cent. from the parablast. Now, of all the tissues of the body, the archiblastic ones have on the whole departed less from the primordial type than any others; hence their cells still retain their primitive powers of growth and reproduction in a higher degree than others. It is to this that I attribute the greater proneness of archiblastic tissues to originate neoplasms under pathological conditions.

Among the parts in which neoplasms very rarely arise are highly specialized structures in general, such as the heart, large blood-vessels, muscles, tendons, ligaments, spleen, urethra, ureter, spinal cord, nerves, etc.

It is also noticeable that obsolete structures very rarely take on the neoplastic process; *e.g.*, the male breast, suprarenals, clitoris, thymus, intervertebral discs, membrana nictitans, uterus masculinus, Meckel's diverticulum, vermiform appendix, urachus, coccyx, os centrale, sesamoid bones, etc.

Herein is further evidence in favor of the view I have advanced, that neoplasms are most prone to arise in the sites of greatest post-embryonic developmental activity.

Throughout the body malignant neoplasms occur with greater relative frequency than non-malignant ones; I have found the ratio to be 64 per cent. of the former, to 36 per cent. of the latter.

Of my 13,824 neoplasms, 7,297 were cancer—males 2,669, and females 4,628—which were distributed as follows:

TABLE II.—SHOWING THE LOCALISATION OF CANCER IN MALES AND FEMALES ON THE PERCENTAGE BASIS.

FEMALES (4,628 CASES).	Per cent.	MALES (2,669 CASES).	Per cent.
Breast	40.3	Tongue and mouth	26.3
Uterus	34.0	Skin	14.3
Rectum	4.3	Lip	12.2
Skin	4.1	Stomach	8.3
External genitalia	3.4	Rectum	7.5
Stomach	2.8	External genitalia	6.8
Liver	2.5	Œsophagus	5.3
Tongue and mouth	2.18	Liver	4.4
Intestines	1.06	Intestines	1.9
Œsophagus	0.70	Breast	0.6
Lip	0.06	Prostate	0.3
All other localities	4.60	All other localities	12.1
	100.00		100.0

This shows that 40.3 per cent. of all cancers in females are of the mammæ, and 34 per cent. of the uterus;* whereas in males only 0.6 per cent. of all their cancers attack the mammæ, and only about 0.3 per cent. the prostate. On the other hand, 26.3 per cent. of all cancers in males affect the tongue and mouth, 14.3 per cent. the skin, and 12.2 per cent. the lower lip; whereas in females only 2.18 per cent. of all their cancers attack the tongue and mouth, 4.1 per cent. the skin, and 0.06 the lower lip.

The same subject, from another standpoint, is further illustrated by the following analysis:

TABLE III.—SHOWING THE LOCALISATION OF CANCER IN BOTH SEXES.

	Males.	Females.	Total.
Breast	16	1,863	1,879
Uterus and prostate	7	1,571	1,578
Tongue and mouth	703	101	804
Skin	381	190	571
Rectum	199	202	401
Stomach	222	130	352
External genitalia	182	158	340
Lip (lower)	326	3	329
Liver	115	113	228
Œsophagus	144	35	179
Intestines	49	49	98
Superior maxilla	42	28	70
Bladder	43	16	59
Testis and ovary	27	27	54
Larynx	34	4	38
Anus	17	10	27
All other localities	162	128	290
Total	2,669	4,628	7,297

This shows that of 1,879 consecutive cases of mammary cancer in both sexes, only 16 were of the male breast, or 1 in 117. According to Paget, 98 cases out of every 100 occur in women. The like peculiarity is noticeable with regard to uterine cancer, for it is met with 224 times oftener than prostatic cancer. In almost all other localities—except the sexual glands, liver, rectum, and intestines, where both sexes are equally liable—the male proclivity to cancer greatly exceeds that of the female. In the lower lip it is 108 times as great, in the tongue and mouth 7 times, in the œsophagus 1.7 times, and in the external genitals 1.2 times.

For comparison with the foregoing clinical data, I append some of the results deducible from examination of the chief mortality returns.

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* I estimate that 1 in 30 of all women of thirty-five years of age and upwards, eventually dies of breast cancer; and 1 in 85 of uterine cancer.

The registrar-general's analysis of the cancer mortality for England and Wales, during the years 1868 and 1888, shows that among females the uterus, etc., was the seat of the disease in 34.7 per cent., the mammæ in 21.2, the stomach in 10.9, and the liver in 9.5 per cent.

From the similar reports of the registrar-general for Ireland, for the years 1887–89, it appears that among women the stomach was the part affected in 22.4 per cent., the mammæ in 21.5, the uterus in 14.1, and the liver in 8.8 per cent.

The Tenth Census Report for the United States indicates that in 33.1 per cent. of the female cancer mortality the uterus was the seat of the disease, the breast being affected in 23, the stomach in 19.9, and the liver in 5.4 per cent.

The Frankfort-on-Main cancer mortality returns, for the thirty years 1860–89, show that the uterus was the seat of the disease in 27.5 per cent. of the female cancer mortality, the stomach in 18.5, the liver in 12.6, and the mammæ in 11.3 per cent.

Among males the English returns indicate that the stomach was affected in 29.6 per cent., the liver in 13.4, the rectum in 8.3, the tongue and mouth in 7.6, the intestines in 5.3, the face in 4.7, the œsophagus in 3.3, the bladder in 2.6, and the lip in 2.4 per cent.

The Irish returns for males show 34.3 per cent. for the stomach, 7.7 per cent. for the liver, 6.4 per cent. for the lip, 6.3 per cent. for the face, 4.6 per cent. for the tongue, and 3.6 per cent. for the rectum.

In the Frankfort statistics the stomach was affected in 29.2 per cent., the liver in 18.6, the intestines in 11.6, the œsophagus and pharynx in 6.5, the bladder, penis, etc., in 4, and the tongue in 2 per cent.

It will be seen that these mortality estimates differ from the clinical data gathered by me, chiefly in that they show much greater frequency of the disease in the stomach, liver, and intestines; and its less frequency in the female breast, skin, tongue, mouth, lips, etc. The ponderous data from which they have been compiled are confessedly not altogether reliable; and it is highly probable that the deaths attributed to cancer of the stomach, liver, and intestines have been exaggerated, owing to diagnostic errors.

In order to show the influence of locality in determining the genesis, structure, qualities, and relative frequency of the different kinds of neoplasms, I have compiled the following tables:

TABLE IV.—SHOWING THE RELATIVE FREQUENCY OF NEOPLASMS IN GENERAL, AS COMPARED WITH THAT OF THE CHIEF LOCAL VARIETIES IN THE TWO SEXES COMBINED.

Kind of neoplasm.	Neoplasms in general. Per cent.	Stomach. Per cent.	Skin. Per cent.	Tongue and mouth. Per cent.	External genitals. Per cent.	Rectum. Per cent.	Lower lip. Per cent.
Cancer...........	54.5	100	42.7	91.36	47.75	85.87	94.32
Sarcoma.........	9.4	Nil.	1.3	1.70	0.42	1.50	1.13
Non-malignant...	24.7	Nil.	12.4	3.87	32.03	12.63	4.26
Cysts...........	11.4	Nil.	33.6	3.07	19.80	Nil.	0.29

TABLE V.—SHOWING THE RELATIVE FREQUENCY OF FEMALE NEOPLASMS IN GENERAL, AS COMPARED WITH THAT OF THE CHIEF LOCAL VARIETIES IN FEMALES.

Kind of neoplasm.	Female neoplasms in general. Per cent.	Uterine neoplasms. Per cent.	Breast neoplasms. Per cent.	Tongue and mouth. Per cent.	External genitals. Per cent.	Skin neoplasms. Per cent.	Ovarian neoplasms. Per cent.
Cancer............	48.7	59.30	77.7	67.79	36.74	34.1	3.36
Sarcoma...........	6.3	.08	3.9	6.04	.70	1.8	2.96
Non-malignant....	33.4	40.54	15.7	12.75	45.35	29.1	.12
Cysts.............	11.6	.08	2.7	13.42	17.21	35.0	93.54

TABLE VI.—SHOWING THE RELATIVE FREQUENCY OF MALE NEOPLASMS IN GENERAL, AS COMPARED WITH THAT OF THE CHIEF LOCAL VARIETIES IN MALES.

Kind of neoplasm.	Male neoplasms in general. Per cent.	Skin neoplasms. Per cent.	Lower lip. Per cent.	Tongue and mouth. Per cent.	External genitals. Per cent.	Rectal neoplasms. Per cent.	Testicular neoplasms. Per cent.
Cancer...........	55.1	48.94	97.03	96.17	64.54	86.15	29.04
Sarcoma...........	13.6	.92	.60	.82	Nil.	2.16	44.09
Non-malignant....	22.7	17.47	2.37	2.05	11.70	11.69	1.07
Cysts.............	8.6	32.67	Nil.	.96	23.76	Nil.	25.80

These data show that the liability of the different organs to evolve the various neoplasms presents extraordinary divergences. Thus, while in some organs certain neoplasms hardly ever arise, these same organs nevertheless often originate other neoplasms, although the latter are of the rarest occurrence in yet other organs. In short, side by side with local predisposition there goes also local immunity.

Thus, although the proneness of the uterus to originate cancer, as compared with its proneness to originate other neoplasms, is above the average for females in general, yet it is much surpassed in this respect by the stomach, mammæ, rectum, tongue, and mouth; on the other hand, the relative liability of the skin and external genitalia is below the average, while that of the ovaries is quite insignificant.

So great is the relative frequency of cancer of the stomach, as compared with its liability to other neoplasms and cysts, that for practical purposes the very existence of these latter may be ignored.

These extraordinary divergences in morbid proclivity are among the most remarkable facts in the whole range of neoplastic pathology; and no doubt the solution of the problem of the origin of neoplasms concentres in them.

It seems to me impossible to account for such vagaries, otherwise than as the result of biological peculiarities inherent to the various tissues of the affected parts. No doubt in every such part there must be corresponding morphological changes, although the microscope has hitherto failed adequately to reveal them. In this connection some recent observations of Ribbert's are of importance; he has shown that cancer is most prone to arise from epithelia in which active mitotic changes are normally always present, or in which such changes manifest themselves under certain conditions (as in the mammæ); whereas in organs whose epithelia seldom exhibit mitoses, such as the kidney, salivary glands, lacrymal gland, thyroid, thymus, male mammæ, etc., cancers seldom arise. These observations give direct anatomical support to the doctrine I have so long advocated on other grounds, viz., that cancers are most prone to arise in localities where cells still capable of growth and development most abound.

Histogenesis.

Inasmuch as every part of the body is liable to its own peculiar forms of cancerous growth; and since the diverse characters manifested by each variety, according to its seat of origin, show that the influence of locality in determining the structure and progress of the disease is very great—it is evident that no study of the life history of neoplastic processes can be complete, which ignores pre-existing structural peculiarities. We must bear in mind that pathological neoplastic products are never of such a monstrous nature as not to present some analogy with the normal structure of the part whence they originate, either in its embryonic or post-embryonic state. It is to be regretted that modern pathologists, in their eager pursuit after microbes, have so far neglected this important consideration, that the links connecting these extremes have, for the most part, still to be ascertained.

Cancer of the Breast.

I will now endeavor to trace, in certain typical instances, the steps by which this transition takes place. I have pointed out, in my work on "Diseases of the Breast" (1894), that the changes underlying the growth, development, and secretion of this organ are but the slightly varied manifestations of embryonic cellular activity, finding expression in different ways; in like manner I maintain that the cancerous processes of the breast are explicable as the outcome of aberrant, imperfect repetitions of these normal processes. Hence the immense majority of its cancerous growths originate from the acini and small ducts; whereas it is very rare for such growths to arise from the skin of the mammary region, the areola, the nipple, or the large ducts.

The histological changes that result in the elaboration of the mammary secretion may be compared with the analogous transformations of the cells of the epidermis, which eventuate in desquamation. Thus milk may be regarded as the product of the deliquescence of successive generations of epithelial cells, which are destroyed in the process, and replaced by relays of new cells, derived from other still active epithelial cells of the part.

But the complete degree of mammary function, which eventuates in lactation, is only periodically attained; and the process is always gradual. As Creighton has shown, subsidence of function goes hand-in-hand with undoing of structure, and revival of function with building up of structure—variations of intensity in the secretory force being measured by its products, which correspond to changing aspects of the secreting acini.

During the intervals between its periods of functional activity, the breast remains in a quiescent, non-secreting state—the *resting stage.* In this condition the gland is shrunken, and almost disappears in the surrounding fibro-fatty tissue. On histological examination, each acinus appears as an alveolar space bounded by a thin layer of fibrous tissue, which, according to Creighton, is denuded of epithelium. Its contents are irregularly arranged, polymorphic, epithelial cells, with large nuclei and scanty surrounding protoplasm. As I shall presently have occasion to point out, this is the structure usually mimicked by mammary cancer.

During the *rising* function the size of the acini gradually increases from that of the resting stage. The cells increase in number and size, and acquire more protoplasm. They gradually arrange themselves so as to form a lining membrane for the wall of the acinus; which, as lactation approaches, is converted into a regular mosaic. The cells become granular, more regular in shape, excavated and vacuolated, secreting granular and mucous fluids. The milk of the first few days is always somewhat crude, containing colostrum cells, which are the last of the long series of secretory products thrown off during the period of rising function.

The *fully expanded acinus* in a state of active secretion is at least four times as large as that of the resting stage. Its contained cells are much more numerous than at any other period; and they form a perfect mosaic, lining the *membrana propria.* Each cell is of polyhedric shape, and has a large nucleus surrounded by a broad zone of protoplasm.

During the period of *subsiding function* the organ gradually reverts to the resting stage, through the converse series of changes. In this process the cells pass through a succession of transformations, from the forms characteristic of the perfect mosaic of lactation, to those peculiar to the various stages of the subsiding process. These changes are accompanied by constant destruction and renewal of the participating cells.

When, during such metamorphoses, the formative activity of the glandular cells predominates over their secretory activity, a dangerous condition is apt to arise; for then, instead of the normal secretion, only cellular products may be formed. Creighton has done excellent service in pointing out how such cells become the germs whence cancers originate. He says: "Taking the breast at the resting state, it cannot under any circumstances reach the perfection of its function without going through the somewhat slow series of unfolding changes. When the evolution that is set up is of a spurious kind; or, in other words, when the gland is disturbed from its resting state by some cause other than pregnancy, the steps of its unfolding are less orderly than in the normal evolution; and the fatality of the morbid process consists in this, that the spurious excitation never carries the gland to the end of its unfolding, or to the perfect function. The products of the gland never get beyond the crude condition; and it is the crude cellular kind of secretory product that makes the tumor."

Cells that should have passed out of the gland as waste products remain at their place of origin, where they proliferate and aggregate more or less independently. It is upon such deviations from the physiological track that the origin of most cancers depends. Neoplasms of this kind generally arise at a time when the breast is undergoing the retrograde changes of the climacteric period, which finally eventuate in the effacement of its secretory mechanism and the withdrawal of its secretory force. Fragments of structure with correlated functional force, surviving the general obsolescence, are the sources to which we must look for the origin of these neoplasms. It makes no difference, in this respect, whether the glandular elements that originate the disease form part of the gland itself, or whether they exist as supernumerary structures sequestrated from the true gland. According to Creighton, the kind of cell most commonly found in such mammary tumors is the large nucleated cell, with scanty surrounding protoplasm. Measured on the physiological scale, these cells belong to the intermediate stage of the unfolding process; they stand for a half-roused physiological stimulus. The morbid force delays at this intermediate stage. The result is the accumulation of cellular waste products instead of true secretion. This accumulation within the acini causes them to become greatly enlarged. Solid bud-like cellular processes arise from their walls, which grow and ramify in the adjacent tissues, in a manner mimicking that of the normal ontogenesis.

In the case of cancer, the process seldom advances much beyond this low grade of organization; but by a kind of continuously progressive gemmation—which is but a superinduced repetition of the initial process—this crude formation grows and reproduces itself indefinitely.

The morbid product, however, always has a certain likeness to the parent tissues. Hence in the breast two types of cancer may be recognized—the *tubular* and the *acinous*. These terms, as applied to mammary cancers, originated with Billroth; but they are used by him in quite a different sense to what I employ them. According to my views, the great majority of breast cancers—about ninety-four per cent.—consist entirely or almost entirely of structures of the acinous type, the tubular form being a comparative rarity. I regard the ordinary alveolar cancer ("scirrhus") as morphologically of the former type, the alveoli and their contents roughly representing acini in the resting stage. The latter term I restrict to certain cancers—histologically often very duct-like in appearance—the true duct cancers. These are usually associated with cysts and intracystic papillary growths, structures hardly ever seen in connection with acinous cancers. The former spring from the mammary ducts, the latter from the acini. All such neoplasms are more or less malignant.

Cancerous tumors are more prone to develop in some parts of the gland than in others. Its periphery, for instance, is a much commoner seat of the disease than its central part. Of 132 cases under my observation, in 90 (68 per cent.) the tumor was *peripheral*, and in 42 (32 per cent.) *central*. This accords with what I have previously pointed out, namely, that the majority of mammary cancers arise in the seats of the greatest post-embryonic developmental activity, where cells still capable of growth and development most abound; that is to say, in the acini, which are much more numerous in the peripheral than in the central part of the gland.

Most of the peripheral tumors are met with in the *upper* and *axillary* mammary segments. Thus in 90 cases under my observation the disease was situated in the *upper* segment in 46, in the *axillary* in 20, in the *lower* in 20, and in the *sternal* in 3. This coincides with the results arrived at by Winiwarter and by Gross. The latter's analysis of the localisation of 820 cancerous tumors may be diagrammatically represented as follows:

		Upper.		
	206	90	55	
Axillary.	83	231	32	*Sternal.*
	32	51	40	
		Lower.		

A considerable number of these peripheral cancers are situated *quite outside the mammary gland*, where, as I have shown, they originate from outlying sequestrated mammary structures. This happened in 13 (9.8 per cent.) out of 132 consecutive breast-cancer cases under my observation. Of 29 neoplasms that originated in this way, 15 were in situation *axillary*, 8 *sternal*, and 6 were found *above* the breast. As I have elsewhere ("Diseases of the Breast," ch. iv.) treated this important subject at some length, I need not further allude to it here.

Nearly all statistics show that in women the *left* breast is more frequently affected than the right. In 151 consecutive cases under my observation, the left breast was the seat of the disease in 56 per cent., and the right in 44 per cent. Of the numerous cases collected by Gross, 869 were of the left breast, and 793 of the right; and in Billroth's practice the proportion was 301 of the left to 279 of the right. In women all other mammary neoplasms manifest the same predilection for the *left* breast, but I have not found this disproportion in males.

A very rare form of initial outbreak is the simultaneous appearance of the disease in *both* breasts. Only 2 instances of this occurred in the 1,664 mammary-cancer cases analysed by Gross.

Cancer of the Uterus.

In like manner, the different parts of the uterus vary greatly in their relative proneness to cancer and other neoplasms. Thus, while countless thousands of cancers have sprung from the uterine *mucosa*, I am not aware of a single instance in which the disease has originated from its peritoneal envelope.

Moreover, the various segments of the uterus itself differ greatly in their relative liability to cancer and other neoplasms. Thus its lower segment (*cervix* and *portio*) is much more apt to generate cancer than its upper segment (*corpus*). Of 160 consecutive cases of uterine cancer under my observation, only 4 were of the *corpus*, or 1 in 40.

What is the explanation of these remarkable diversities in morbid proclivity? We must, I think, seek an answer to this question in the biological peculiarities inherent to the affected parts, and in their concomitant developmental and structural diversities, all of which are ultimately ascribable to functional modifications.

The classification of uterine cancers may best be based upon their histogenesis. Accordingly, the different varieties are determined by the type of epithelium whence they originate; that is to say, they are either of the *cylinder-celled, squamous-celled,* or *endothelial* variety. The old terms "scirrhus" and "encephaloid," as applied to cancerous tumors, have now become misleading and obsolete.

According to my observations, the great majority of uterine cancers (about ninety per cent.) are of the cylinder-celled variety, which must therefore be regarded as the typical form in this organ.

Since both cylindrical and squamous epithelium may be met with in each uterine segment—corpus, cervix, and portio—so likewise each of these parts may originate both varieties of cancer. While, however, cylinder-celled cancer arises with predominating frequency, alike in the cervix, portio, and corpus, it is most exceptional for squamous-celled cancer to take origin in the corpus.

It has been clearly demonstrated that cancer of the corpus is much less common than cancer of either the cervix or portio; but a question of some difficulty arises, as to the relative proneness of the cervix and portio to originate the disease. Most pathologists consider the cervix to be the more liable, and in this I concur.

Cancer of the *portio* may start at any point between the os and the fornix of the vagina; but it is in the former vicinity that the majority of cases arise. In the *corpus* the disease originates oftener in the region of the fundus and its vicinity than elsewhere.

It seems certain that the immense majority of uterine cancers arise from the glands of the cervix or their aberrant extensions. Among the latter the ovula Nabothii must be included.

The epithelia of the affected gland grow and multiply with undue rapidity, and at the same time the cells become greatly elongated. Cornil has observed their nuclei in various stages of karyokinesis; and individual cells may commonly be seen containing more than a single nucleus.

In consequence of these changes, the epithelial cells at the seat of the disease become unduly numerous and acquire a stratified arrangement, encroaching on the lumen of the gland, which they often completely obliterate. The newly formed cells lose their typical shape—polyhedric, irregular, and quasi-flattened forms predominating; and cilia are never seen. Thus the diseased gland is converted into a club-shaped mass of proliferating polymorphic cells, of which only the peripheral layer retains the original cylindrical form. Here and there bud-shaped collections of proliferous cells pressing on the membrana propria cause it to bulge outwards and eventually to disappear; and a similar fate overtakes the layer of flattened cells immediately external to it. While this is going on a great concentration of small round cells takes place in the stroma, in the vicinity of the morbid process. Meanwhile, solid processes of proliferous epithelial cells sprout out, forming narrow branching columns which, as they penetrate the adjacent structures, anastomose and form an irregular network. By the repetition and further extension of this process, the cancerous tumor is formed. Often, even in fully evolved cancers, the epithelial columns retain their solid form; but in most cases they eventually develop lumina, lined by one or more layers of columnar cells, as in the so-called malignant adenoma.* It will be gathered from the foregoing that the process by which these varieties of cancer arise is but an aberrant, superinduced repetition of the normal developmental process.

It is probable also that cancer of the cervix may sometimes arise from residua of the Wolffian and Müllerian ducts, such as Tourneaux and Legay have found embedded in the cervical tissues.

In the development of papillated structures like the portio and cutis vera, the epidermis plays an important part. It causes these structures to arise by processes of its proliferous cells growing into the subjacent connective tissue. The chief morphological feature that marks the transformation of simple epithelial hyperplasia into epithelial cancer consists essentially in an indefinitely sustained, superinduced repetition of the above process. Just in the same way cancer of the portio begins by proliferous cells of the interpapillary region of the rete mucosum growing into the subjacent fibrous stroma, where knobby projections are at first formed, and subsequently ingrowing columns. These cells multiply and develop in semi-independence, regardless of the requirements of adjacent parts and of the organism as a whole. In the less grave form of the disease the new formation does not progress beyond this initial stage. The ingrowing cells preserve their normal form, and their mutual arrangement is but little altered; the ingrowing columns fail to penetrate deeply; the malady progresses slowly, and dissemination is rare. This is the tubular variety. In the graver form the departure from the normal is more decided, changes take place in the grouping of the cells, and "nests" are formed; the ingrowing columns increase rapidly and penetrate deeply; they branch and anastomose, and sooner or later there usually is dissemination. This is the lobular variety.

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* Probably most of the new formations thus designated by German pathologists are instances of glandular hyperplasia rather than of cancer. The term "adenoma malignum" is a monstrosity of pathological nomenclature that ought to be sharply repudiated, notwithstanding its modernity.

Such are the varieties of cancer that arise from the portio—properly so-called; but, in addition to these, other forms of cancer also take origin from this part. Under certain pseudo-pathological conditions, which I will now proceed to describe, the cylindrical epithelium of the cervix encroaches upon the epidermis-covered territory of the portio; and from this foreign element cylinder-celled cancers arise, analogous to those that spring from the cervix. So common is this invasion of the portio that the majority of its cancers originate from this source.

It seems probable that most of these aberrant elements are the outcome of developmental irregularities. At an early stage of embryonic life, the upper part of the vagina—as well as the cervix—is lined by cylindrical epithelium. In the subsequent transformation to the flattened variety, minute islets of the original cylindrical cells may still persist unchanged. Klotz and others have demonstrated conditions of this kind in adults; while Fischel has shown that in young infants cylindrical epithelium is usually found occupying the portio for a considerable distance external to the os externum.

Here mention must also be made of the invasion of the portio by offsets of the cervical glands (the so-called "erosions"), that so frequently appear during post-embryonic life in consequence of hyperplastic changes; as well to the somewhat similar conditions that ensue from partial prolapse ("ectropion") of the cervical mucosa, whether the result merely of tears during parturition, of cystic disease, or of other pathological states. Moreover, ovula Nabothii not infrequently project on the free surface of the portio. Recent researches seem to indicate that most of these acquired forms of heterotopia are also really of congenital origin, the inherent flaw simply being made manifest by the supervention of other pathological changes. Even "lacerations" of the cervix may often be of embryonic origin; for Fischel has demonstrated the occurrence of congenital fissures in exactly the situations usually occupied by these so-called lacerations.

Such are the cellular elements that play the chief rôle in the pathogenesis of cancer of the portio. The stages of the process by which from these aberrant cylindrical cells glandular cancer develops, are identical with those by which the disease arises from the glands of the cervix.

Similarly heterotopic epidermoidal cells are often found at some distance from their normal habitat—the portio. Detached epithelial "pearls"—*sequestra* of the epidermis—are of common occurrence in the vaginal aspect of the portio, beneath the corium. In young nulliparæ the line of junction between the epidermoidal cells of the portio and the columnar cells of the cervix coincides with the os externum. In multiparæ, however, the os is seldom thus situated; for in them flattened cells of the portio are prolonged for a variable—often considerable — distance within the cervical canal.* In exceptional instances cells of this kind have been met with even within the corpus (Ries, Schuchardt, Fritsch). From the foregoing it will be gathered that the exact situation of the line of epithelial demarcation is variable, and that the different epithelia are more or less intermixed for some distance on either side of it. It is in connection with these aberrant elements that primary epidermoidal-celled cancers of the cervix and corpus arise. In the latter situation this variety of cancer is very rare, but examples of it have been reported by Gellhorn, Flaischlen, Piering, Gebhard, and others.

Most cancers of the corpus uteri, however, originate from the utricular glands; and the steps of the process are so similar to those by which cervical cancers arise that no further account of them need here be given. It should, however, be mentioned, that the normal cells of these glands differ from those lining the cervical glands, in that they bear cilia (Cornil, De Sinéty, Friedländer); moreover, they never present calyciform characters. According to Cornil, in the hyperplastic new formations of the uterine mucosa, the cilia of the glandular epithelium usually persist, and the layer of flattened periglandular cells is augmented; whereas, in incipient cancer, both the cilia and the periglandular cells disappear. Waring has demonstrated the important fact that the constituent cells of cancers of the pancreas and stomach produce the same ferments—trypsin, pepsin, etc.—as the normal secretory cells of these organs. It is highly probable that, if similarly investigated, cancers of the cervix would be found to present indications of substances identical with the cervical mucus, and that they would differ from cancers of the corpus in this respect. It accords with the foregoing that Cornil and others have observed the constituent cells of cervical cancers undergoing mucoid and calyciform changes, similar to those that are so characteristic of the cells of the cervical glands, which are indicative of the elaboration of their peculiar secretion.

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* Villiers and Thérèse have lately demonstrated the existence of islets of epidermoidal cells with Malpighian stratum, etc., which presented as whitish plaques in the midst of the cervical mucosa.

CANCER OF OTHER PARTS OF THE BODY.

In other parts of the body similar conditions prevail. Thus, in the *tongue* I find that cancer invariably arises from the interpapillary processes of the Malpighian stratum, and is therefore always of the epidermoidal-celled variety. The numerous glandular structures of this organ seem hardly ever to originate cancer.

I have found the seats of the initial lesions of cancer of the tongue and mouth in 100 consecutive male cases to be as follows:

Edge of tongue* (middle, 21; base, 14; tip, 5; front, 4)	in	48	cases.
Floor of mouth (near frænum)	"	21	"
Buccal surface of cheek	"	10	"
Gum	"	5	"
Dorsum of tongue	"	4	"
Empty socket of molar tooth	"	2	"
Soft palate	"	2	"
Hard palate	"	2	"
Floor of mouth (other than near frænum)	"	2	"
Substance of tongue	"	2	"
Between gum and cheek	"	1	case.
Between gum and lower lip	"	1	"
Total		100	cases.

In the *skin* similar peculiarities are noticeable, but in a larger proportion of cases the disease seems to start from the glandular structures. Of 49 consecutive cases of cutaneous cancer of which I have preserved the records, 37 originated from the head, 1 from the neck, 2 from the trunk, 7 from a lower limb, and 2 from an upper limb.

Of the 37 head cases, 23 originated in the nose (near the inner canthus, 10; the ala, 3; between the two foregoing, 5; tip of nose, 3; root, 1; middle of bridge, 1), 6 from the cheek, 3 from the lower eyelid, 2 from the forehead, 2 from the skin of the upper lip, and 1 from the external ear. The great predisposition of the skin of the face, especially that of the nose and its vicinity, to develop cancer is very remarkable.

Of the 7 cases of cancer of the lower limb, 4 sprang from the thigh, 2 from the foot, and 1 from the knee.

Of the 2 upper-limb cancers, 1 was of the axilla and the other of the hand.

Of the 2 trunk cancers, 1 sprang from the skin of the back and the other from that of the front of the abdomen.

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* Right side, 25; left side, 18.

The Primary Neoplasm.

In a typical case of cancer the disease presents as a solitary, nodulated, solid tumor, of a more or less firm texture. Although we know from histology the infiltrating character of such a growth, yet to the unaided senses it generally seems to be a more or less circumscribed mass. On careful examination of its periphery no capsule can be made out, and it will be seen that the passage from the diseased to the healthy tissue is by no means sharply defined—the irregularly growing edge of the cancer is, so to speak, dovetailed into the surrounding preëxisting tissues.

In describing mammary cancer, Astley Cooper says: "I would observe that the scirrhous tumor is not all of the disease; there are roots which extend to a considerable distance, and those who gave the disease the name of cancer probably knew more of its nature than we are disposed to give them credit for. It is supposed by some that this name was given on account of the appearance of the surrounding veins. I should rather say it was from the appearances on dissection than from anything without. When you dissect a scirrhous tumor, you see a number of roots proceeding to a considerable distance; and if you remove the tumor only, and not the roots, there will be little advantage from the operation; no glandular structure nor any of the roots should be allowed to remain."

This admirable *résumé* of the subject is entirely in accord with the results of modern research.

If we examine the growing edge of a mammary cancer, we shall find that one way in which the disease progresses is by the continuous centrifugal extension of ingrowing epithelial processes. These spread most rapidly in the directions of least resistance, which are usually along the adjacent lymphatics and perivascular sheaths. These Köster has found distended with cancer cells. Fine, elongated, cord-like processes of cancerous growth thus arise, which often extend from the parent tumor far into the surrounding tissues, especially posteriorly. In this connection nodular growths often develop which, to the naked eye, may appear to have no connection with the primary tumor. In addition to these there are frequently found in the vicinity of the latter really discontinuous nodules, which are the first signs of regional dissemination. Besides the foregoing, small, discontinuous, satellite nodules are occasionally found in the vicinity of the main tumor, which probably arise as spontaneous outbreaks of the disease in outlying proliferating acini. These indicate that the tendency to cancer formation extends beyond the immediate limits of the initial lesion; and from their presence we may infer *regional* as well as *structural* proclivity.

In the cylinder-celled uterine cancer, the disease usually assumes the form of a more or less projecting, flattened, quasi-circumscribed, fungoid excrescence. Such tumors are elastic in consistence, very friable, of great vascularity, and their surface often presents irregular bosses. By the continuous centrifugal extension of proliferous epithelial processes, derived from the growing margin of the neoplasm, such tumors increase in size. In their genesis and subsequent development, these epithelial offshoots repeat the various stages of the initial morbid process. Where the tissues of the uterine wall come into contact with the advancing neoplasm, they are interpenetrated by its ingrowing processes, which spread with special facility along the lymphatics and perivascular sheaths. The extent to which this takes place is variable, some growths manifesting a tendency to burrow from the first, while in others the tendency is rather to project from the free surface. In the cervical wall this invasion causes the tumid and indurated condition of the part, that is so often noticeable on vaginal examination. Blocking of the veins and consequent venous engorgement is also an important factor in the production of this tumidity, especially in the uninfiltrated parts of the organ and their vicinity.

It will be gathered from what has been stated that the integration of cancerous growths is very inferior to that of normal parts. New centres of development are constantly arising among their constituent proliferating cells; so that, before the initial growth has made much progress, numerous subsidiary centres of morbid activity have arisen in it or in its vicinity.

The effect of cancerous growths on the tissues in the midst of which they develop is to cause their destruction by pressure atrophy. Francotte and de Rechter have lately made a special study of the changes that take place in the nerves under these circumstances. They find that the endoneurial connective tissue is much thickened and assumes a lamellar disposition, owing to the proliferation of its constituent cellular elements; while the axis cylinders, being thereby compressed, atrophy and gradually disappear.

The gross features of cancerous tumors are largely determined by the structure of the part whence they originate; hence hard cancers are the dominant forms that arise from parts rich in fibrous tissue.

Thus the characteristic hardness (*scirrhus* *) of mammary cancers is mainly due to the density, toughness, and abundance of the fibrous stroma of the gland. On making a section through such a growth, a crisp, creaking sensation is experienced; and the cut surface "cups," presenting a glistening, whitish, fibroid aspect, interspersed with small, yellowish, opaque spots. The appearance has not inaptly been compared to that of a section of an unripe pear (*apinoid*).

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* This term was used by Galen (*σκίῤῥος*, from *σκίρος*, a piece of marble) as synonymous with *σκλήρωμα*—hardness. It was applied by him and his successors to all hard tumors; subsequently its application was limited to indurations having a special tendency to terminate in intractable ulceration, and so eventually to hard cancer.

Cancers of the uterine mucosa are very different from this. Such growths form succulent masses, of whitish, pale yellowish, or pinkish aspect, elastic in consistence, very friable, and of great vascularity. Neither hardness nor "cupping" is noticeable, on account of the scantiness of the stroma, on the presence of which these properties depend.

Yellowish, opaque areas—most abundant at the central and older part of the growth—are met with in all cancers; and they are due to degenerative changes in their constituent cells. The more recently formed peripheral parts of such neoplasms often present a semitranslucent aspect. On scraping the cut surface of a cancerous tumor, a milky fluid is obtained—the so-called "cancer juice"—which consists of morbid epithelial cells in an albuminous fluid. The section nearly always presents a solid appearance, cysts being seldom met with.

Under the microscope sections of mammary cancer are seen to consist of ovoid or irregularly rounded, solid masses of epithelial cells, enclosed in corresponding alveolar spaces, bounded by thick walls of fibrous tissue.

Cancers of the uterine mucosa, on the other hand, consist of irregular congeries of large, more or less tubuliform structures, distended to various irregular degrees with epithelial cells, embedded in scanty fibrillar stroma. They are seen cut in diverse planes. Within most of them a small lumen can be made out; but not infrequently they are quite solid. Small, polypoid, epithelial excrescences sometimes project into the lumina. Rarely the cancerous tubuli are lined by but a single layer of columnar epithelium.

In their entirety the cancerous cells form branching, racemose masses, ingrowing into the surrounding stroma. By serial sections of such tumors, after the manner adopted by embryologists, Hauser has lately demonstrated in cancer of the stomach that the appearance of closed alveoli is really deceptive; the spaces that appear to be such are really nothing more than sections of the branching epithelial ingrowths, which are directly continuous with the glandular structures whence they arose.

Such tumors increase in size by the continuously progressive ingrowing of the budding epithelial masses. Altogether the pathological appearances present striking resemblance to those seen during certain stages of the ontogeny of the corresponding normal structures.

The shape and size of the constituent cells of cancerous neoplasms, and their grouping, vary according to the locality affected; but some resemblance is always noticeable, in these respects, between the pathological new formation and its anatomical prototype.

In cancer of the breast these cells vary much in size and shape, and they usually have no definite arrangement—being irregularly crowded together within the meshes of the stroma; yet the varieties met with are not unparallelled by what is seen in the cells of the normal acini during certain phases of the physiological evolution.

Moreover, it is a striking fact that the peripheral cells of newly formed cancer alveoli often present well-marked resemblance in shape and arrangement to the cells of normal acini. This condition, as Morton has pointed out, occasionally persists; and even distinct lumina may be formed. Thus the cells of the cancer alveoli are evidently but the slightly altered descendants of the secretory cells of the gland; hence their tendency to revert to the parental type, which is always obvious. The polymorphism of the cells of acinous cancer of the breast, when not thus accountable, is simply a pressure effect, owing to the rapidly increasing cells being cramped by the density of the surrounding stroma; so that it is seldom seen, to the same extent, in cancers of other parts.

In cancer of the uterine mucosa the constituent cells of the cancerous tubuli are generally multilaminated, the peripheral ones often being of columnar type, and arranged perpendicularly to the surface of implantation, as in the normal uterine glands. The rest of their cells are of various irregular shapes and sizes, most of them being polyhedric or quasi-flattened. The cancer cells are invariably devoid of cilia, even when these exist in their physiological prototypes; whereas, in the various phases of "glandular endometritis," the cilia, if present in the normal cells, are often still retained (Cornil). The cancer cells are much more easily detachable than their congeners of the normal glands; hence, in cutting sections of uterine cancers for microscopical examination, great care must be exercised lest they all fall out. Thus these cells are evidently but the slightly altered descendants of the epithelium of the affected utricular glands; and in many cases the various transitional stages from healthy glands to cancerous tubuli can be distinctly made out. Altogether, the pathological appearances present striking resemblances to those observed during certain stages of the development of the utricular glands, of which they may be regarded as a modified superinduced repetition.

Waring has demonstrated the important fact that the constituent cells of cancers of the stomach and pancreas produce the same ferments—pepsin, trypsin, etc.—as the normal secretory cells of these organs. In like manner Johannes Müller, more than half a century ago, demonstrated the presence of casein in breast cancers; and the abundance of fatty matters contained in the cells of such neoplasms is well known. We are thus reminded of the similar metamorphoses that the cells of the normal gland undergo during lactation; but the nearest approach to normal secretion that the pathological structure ever produces is a scanty mucoid fluid. This accords with some experiments by Martinotti, which go to show that glandular cells in a state of active growth and proliferation tend to lose their normal functional aptitudes, there being a certain antagonism between proliferative and secretory changes.

Similarly cancers of the cervix uteri may be expected to yield indications of the presence of substances identical with the cervical mucus; and in this respect they will probably be found to differ from cancers of the corpus. As tending to confirm this expectation, it may be mentioned that Cornil and others have observed in the constituent cells of cervical cancers indications of mucoid or calyciform changes, similar to those that are so characteristic of the epithelium of the cervical glands during the elaboration of their peculiar secretion.

The essential factor underlying the increase of cancerous neoplasms is the continuous growth and proliferation of their constituent epithelial elements. The pathological cells multiply, like their physiological prototypes, chiefly by indirect nuclear division; and the similarity extends even to the details of karyokinesis—equatorial plates, achromatic spindles, etc. Thus the component cells of a cancerous tumor are the direct descendants of the primary neoplastic cells. It has been stated that the latter, by a kind of spermatic influence, infect adjacent cells, and so excite in them morbid action similar to their own. This conception appears to me to be based upon complete misunderstanding as to the true nature of spermatic influence; and the appearances actually observed afford it no support. The nuclei of cancer cells are larger, richer in chromatin, and they more frequently originate karyokinetic figures than do their physiological prototypes. More than a single nucleus is commonly noticeable in them; and the nuclei often shed their chromatin into the surrounding protoplasm, as a sort of preliminary to division—whereby the so-called "giant cells of cancer" arise. Hypo- and hyperchromatic conditions of the nucleus are frequently met with. Asymmetrical and multipolar mitoses also occur with undue frequency, and the axis of cellular division is often displaced from its normal plane. Moreover, abortive mitoses are not uncommon. Nuclear fragments, detached during mitotic changes, probably originate the "corps colorables" described by Foà and others. Such conditions are most marked when the disease is in active progress. Vacuolation is of common occurrence.

Cancer cells are short-lived, for they are soon overtaken and destroyed by various degenerative changes. Fatty and hyaline metamorphoses are the commonest. The colloid change is rarer; and still more rarely do the cells calcify, forming the so-called sand grains ("Sandkörner," "corps calcaires," etc.), as in cases described by Ackermann, Neugebauer, and others.

With regard to the significance of the various pseudoparasitic bodies found in cancer cells, I need here add nothing to what has been stated in the preceding section.

It was formerly believed that many of the above conditions were specially characteristic of cancer, but it is now known that similar changes are met with in the growing parts of sarcomatous and even of non-malignant neoplasms. In the process of repair after wounds, similar changes are noticeable. Moreover, the experiments of Pierallini and D'Arcy Power as to the effects produced by irritation upon living tissues show that in consequence of various artificial stimulations similar conditions ensue.

Taken in their entirety, these deviations from the normal are but the morphological expressions of a high degree of reproductive activity, which is an essential characteristic of cancer cells. This phenomenon seems to me to be of the same nature—in exaggerated degree—as the accelerated proliferation of epithelial cells noticeable in the process of repair of wounded epithelial surfaces. Just as this exceeds the physiological rate of increase requisite to maintain the normal *status*, so the former exceeds the latter; but I believe all these manifestations belong to the same order of events. The wonderful reproductive activity of cancer cells enables us to understand how a single such cell may be the germ of a large tumor—even the largest. It is chiefly in this respect that cancer cells differ from normal epithelial cells. In their young state, as Klebs, Waldeyer, and others have observed, both possess contractile and locomotor properties.

It will be gathered from what has been stated that cancer cells grow and multiply more rapidly than their physiological congeners, while at the same time their vitality is less stable and their developmental power less complete.

The presence of various non-specific pathogenic microbes in cancerous growths has been shown by many pathologists to be of common occurrence. Verneuil, having noticed the frequent septic infection of operation wounds after the removal of cancerous tumors, was led to examine the latter for bacteria; and in the softened areas he found various kinds of bacilli and micrococci in abundance. Zahn, by cultivation experiments, has shown that microbes abound in cancer metastases, even when the latter are not in direct communication with the surface of the body. To account for this, Hauser supposes that they were carried there along with cancer cells detached from the primary focus.

Bodies like yeast fungi (*blastomycetes*) are also often present, but no evidence of any value has hitherto been adduced as to their etiological significance.

Leucocytes and red blood corpuscles have often been detected between closely approximated cancer cells, and even within them. The invagination of one or more cells within another has actually been seen to occur by several good observers. It is easy to mistake cells of this kind for parasites, especially when they have undergone degenerative changes. The presence of leucocytes between and within cancer cells is most noticeable in inflamed areas. Ströbe maintains that this indicates a kind of phagocytosis. In the vicinity of actively growing cancer, the stroma is invariably infiltrated with numerous small, round, nucleated cells.

It has been demonstrated by Ide and others, that the cells of the normal epidermis and those of cutaneous epitheliomas, instead of being completely isolated, as hitherto believed, communicate freely with their neighbors by small bridges—"ponts intercellulaires"—in which both cell membrane and protoplasm are involved, and sometimes even nuclear filaments.* The cells of the mammary epithelium, being derivatives of the epidermis, are probably similarly related. Barfurth has shown that the epithelial cells of the uterine mucosa are thus united.

In cancer of the breast, however, the constituent epithelial cells usually hold together much less firmly than do those of the normal gland; in fact, they frequently seem to be completely detached and immersed in the albuminous fluid within the alveoli. This want of cohesion between their constituent cells is probably one of the chief reasons why mammary cancers disseminate so much more frequently than similar neoplasms in most other localities.

Another point of resemblance is in the distribution of the blood-vessels and nerves, neither of which are found within cancer alveoli any more than they are within the corresponding normal structures. Moreover, so far as is known, the relations of both to the lymphatic system are very similar; for, as De Sinéty has shown, within the *membrana propria* of the normal mammary acini there exists an imperfect lining of endothelial cells, which is probably a derivative of the lymphatic system; and Cornil and Ranvier—by injection of Prussian blue and nitrate-of-silver staining—have demonstrated that in mammary cancer the alveoli are in direct communication with the lymphatic radicles. It is noteworthy that the endothelial cells of the latter take no part in the cancerous process.

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* Barfurth has lately shown that the epithelial cells of the uterine mucosa are knit together in this way.

From the foregoing we learn that there is nothing specific about cancer cells and structures, as was formerly believed; there is departure from the normal type of development, but no foreign structures are produced. Thus, it is chiefly on account of the greatly increased numbers of their constituent cells, of their disorderly grouping, of the comparatively imperfect degree of development attained, and of their less stable vitality that cancerous structures differ from their normal prototypes.

The characteristics of the stroma of cancerous tumors are chiefly determined by the preëxisting structure of the affected part. Its alveolar disposition, which was formerly regarded as the histological criterion of cancer, is now known to be merely a local peculiarity. In many acute forms of the disease alveolar arrangement is altogether wanting, the cells being diffused, often in single rows, between the fibrils of the stroma.

In its minute structure and general characters, the stroma of mammary cancer closely resembles the stroma of the normal gland, of which it is evidently a derivative. It consists of thick bands of dense white fibrous tissue, containing elastic fibres and anastomosing connective-tissue cells, which are specially numerous at the meeting points of the diverging bands. The characteristic hardness of mammary cancers is mainly due to its abundance and density; in fact, hard cancers are the dominant forms that arise from regions rich in fibrous tissue. Moreover, it is noticeable that elastic fibres are met with in great abundance in cancers that arise from structures normally rich in them, such as the breast and skin. Müller attributes the large amount of gelatin found on analysis in mammary cancers to the abundance of its fibrous stroma.

On the other hand, the stroma of uterine cancers consists of scanty fibrillar tissue, like that met with in the normal uterine mucosa, which it further resembles in that it usually contains unstriped muscle cells. Hence little or no gelatin is found in uterine cancers.

The question has been much discussed, whether the cancer stroma is of new formation or simply the modified preëxisting structure.

It seems almost certain, from various considerations, that it is largely of new formation. In the case of mammary cancer, coincidently with the initial proliferation of the cells within the pathological acinus there appears an infiltration of the periacinous connective tissue with small round cells. Ribbert and some others maintain that this active increase of the cells in the subepithelial connective tissue, precedes the proliferation of the epithelial cells, and is the initial cancerous change. It is from this embryonic parablastic tissue that the newly formed cancer stroma is chiefly developed. The constant presence of these cells in the stroma is an important factor. By some pathologists they are regarded merely as leucocytes, derived from the bloodvessels of the stroma as the result of chronic inflammation; but from their periacinous rather than perivascular grouping, and from their anatomical characteristics, it is more probable that they arise as the outcome of the developmental rather than of the inflammatory process. They consist mainly of nuclear substance. It must be remembered that the mammary acini and small ducts are normally surrounded by a layer of immature connective tissue, rich in cells, and it is from this source that these parablastic elements probably arise. They are, in fact, the product of the reawakened activity of the cellular elements of the locality. Their presence in the cancer stroma indicates that the latter is an imperfect formation. An extreme degree of the same condition is seen when the stroma does not evolve beyond the myxomatous stage, as in the rare variety of the disease called *carcinoma myxomatodes*. In like manner the presence of spindle cells in the stroma may be explained. Hansemann, who has made a special study of the cells in the cancer stroma, describes four different kinds: 1. Fusiform and stellate cells, the ordinary connective-tissue cells. 2. Flattened epithelioid cells arranged around the walls of the lymphatic canaliculi. 3. Cells with large deeply staining nuclei and little protoplasm—lymphocytes. 4. Cells with lobulated or budding nuclei—leucocytes—emigrant white blood corpuscles. He has often met with mitotic figures in connection with the multiplication of these cells.

Within the cancer stroma numerous small *arteries, veins,* and *capillaries* ramify, most of which are derived by new formation from the preëxisting vessels of the part. Hence the degree of vascularity in cancers of different organs is very variable; and even in different parts of the same neoplasm similar irregularities are often noticeable. As in the embryonic development, the nascent cancer is at first nonvascular; it is only at a later period that vessels spread to it from the adjacent vascular system. These have been injected by Thiersch, Billroth, and others, and found to form networks of similar form to the alveoli. They are generally larger and less regular in their calibre and arrangement than the corresponding normal blood-vessels, tortuous dilatations and small sacculations being of frequent occurrence. According to Quénu, their walls are often thickened and their lumina occluded, in consequence of chronic endarteritis. These lesions are occasionally so marked as to produce a telangiectasic condition. While the vascular system of cancers can be readily injected by the arteries—even the smallest—it is generally difficult to do so by the veins, the substance injected then finding its way into the circumferential venous system, instead of into that of the neoplasm. This is probably due to the frequent blocking of the veins by the growth of the neoplasm, by thrombi, etc. Thus may be explained the venous engorgement that is almost invariably associated with cancer.

Accompanying the stromal blood-vessels are numerous *lymphatics*, which have been injected, and their distribution studied by Schröder van der Kolk, Krause, Rindfleisch, and others. In the case of mammary cancer, as previously mentioned, their radicles are in direct communication with the alveoli; a similar condition probably holds for other forms of cancer. This enables us to understand the great frequency of dissemination in the lymphatic glands.

Cancers are generally regarded as *nerveless;* but vasomotor filaments probably accompany the stromal blood-vessels, although this is denied by Verneuil and Nepveu. Our knowledge of this subject is singularly inadequate, and there is here need of further research.*

The presence in the cancer stroma of such foreign elements as cartilage, bone, ossiform and calcareous matter, has been demonstrated in several instances; moreover, similar heterotopic structures have also been met with in sarcomatous and non-malignant neoplasms, as well as in parts otherwise free from any disease. The most feasible explanation of the presence of these anomalous structures in such situations is that which ascribes their origin to sequestration of small portions of the matrix of the evolving thoracic skeleton at an early developmental stage.

Foreign structures of this kind have been found in association with mammary cancers by Coen, Hacker, Warren, Heurtaux, Wagner, and Busch. In the otherwise normal breast, similar structures have been met with by Rindfleisch and Hacker. Instances of their association with mammary sarcomata have been reported by Arnold, Pilliet, Coats, Bowlby, Stilling, Battle, Durham, and others; with mammary myxomata by Billroth, Leloir, and others. Instances of the extensive calcification of sarcomatous mammary tumors have been recorded by Dubar and Clarke. In this connection it may be mentioned that Bryk and Bérard have seen complete calcification of the otherwise normal mamma.

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*This subject has recently been investigated by H. Young who has found nerve filaments present in breast cancers and in most malignant tumors. In cancers he thinks it probable that the included nerves are branches of those normally existing in the invaded tissues; but in sarcomata the nerves seemed to form an integral part of the tumor. They generally accompany the blood-vessels, and they probably belong to the vasomotor system.

In fibroadenomata similar conditions have been met with. It seems certain that the various non-malignant cartilaginous and ossifying tumors, found in the breast by Leser, Pied, Hacker, Lange, Cruveilhier, Astley Cooper, and others, originated from aberrant elements of this kind.

In the mammæ of various animals—but especially of bitches—cartilage-containing tumors are of frequent occurrence, and they are often associated with malignant disease.

The presence of such heterotopic structures in neoplasms is of great interest, as indicating genetic connection with embryonic developmental irregularities (*vitium primæ formationis*).

The *chemical analysis* of cancerous growths—much neglected of late—has hitherto failed to reveal the presence of any specific morbid substance. Albuminous constituents predominate. Detailed analyses may be found in the works of Lebert, Walshe, and Müller; I am not aware of any recent publications of this kind.

It has lately been shown that glycogen is invariably present; and, according to Freund, so is sugar. Glycogen is most abundant in the rapidly growing forms of the disease. In this respect cancer elements resemble embryonic structures in general, which are always rich in glycogen. Beneke has found an abundance of cholesterin and myelin.

Albumoses seem to be completely absent (Hewlett, Brodie), whereas in cultures of pathogenic bacteria such substances abound. It should, however, be mentioned that Meyer has found splenic extracts from cancerous subjects of double the toxicity met with in other cachectic states. Brodie failed to find even a trace of either chitin or cellulose in cancerous tumors, which seems to indicate the absence of encapsulated protozoa.

Hewlett's investigations show that the cells of cancer, sarcoma, and adenoma contain about the same amount of phosphorus as those of the normal tissues; that there is no special distribution of iron in these tumors, their cells being neither richer nor poorer in this respect than the ordinary tissue cells; and that the proteids of cancer, like those of other cellular organs, consist chiefly of nucleoalbumin.

Reference has elsewhere been made to Waring's important researches on the physiological properties of carcinomata.

According to recent observations, the juice of perfectly fresh mammary cancers is of an alkaline or neutral reaction; whereas, within a few hours after death, the reaction becomes acid.

In many parts of the body, such as the buccal cavity, the outbreak of cancer is commonly preceded by obvious hyperplastic changes (ichthyosis) in the surface epithelia. Moreover, it is noticeable that these lesions are seldom limited to the precise starting-point of the cancerous disease. This clearly implies that the abnormal activity, which at a given spot culminates in cancer, affects in a less degree the adjacent epithelia of the region for a considerable extent. The question arises whether all parts of the body, in which cancers arise, are not similarly circumstanced. The indications at present forthcoming are decidedly in favor of an affirmative answer; the admirable researches of Heidenhain have, at any rate, answered the question in this sense for the female breast. He has conclusively shown that every mamma containing a cancerous tumor is diseased throughout. Its secretory cells are unduly numerous, and they everywhere show signs of excessive reproductive activity; while the peri-acinous connective tissue is much increased, its nuclei are unduly abundant, and it is infiltrated with small round cells. Parts in such a condition are evidently more prone to originate cancer than perfectly normal structures. Heidenhain is no doubt right in maintaining that proliferating acini of this kind, left behind at the primary operation, are the germs whence most *late* recurrences arise.

In like manner the *mucosa* of a cancerous uterus is never in a healthy condition. As a rule it is markedly thickened; and lately a great deal of attention has been given to ascertain the nature of this thickening, which may assume a spongy, fungoid, or villous aspect—with the formation of distinct mucous polypi in some cases. Histological examination reveals hyperplastic lesions, similar to those met with in the so-called "chronic glandular endometritis," the stress of the morbid process usually falling on the glands. After a time the musculature also becomes hypertrophied. It is probable that most *diffuse* uterine cancers arise as the exaggerated outcome of similar lesions.

Local Dissemination.

Heidenhain has shown that the loose areolar tissue intervening between the mammary gland and the pectoralis major muscle, contains numerous glandular offshoots and lymphatics, which in cancer cases are nearly always diseased. Some of these not only adhere to the fascia over the muscle, but often penetrate it, and even become embedded in the muscle itself. In the ordinary operation of amputation of the breast, these structures are almost invariably cut off and left behind. On careful examination after removal, Heidenhain found that the disease had not been completely extirpated from this situation in twelve out of eighteen breasts consecutively amputated for cancer; and he predicted recurrences, which soon followed. To obviate this he recommends that the fascia over the pectoralis major muscle, and a layer of the subjacent muscular substance, should be removed in every case, together with the diseased breast; and I certainly think this recommendation ought to be regarded as an essential feature of the operation.

It is, however, noticeable that gross adhesions between the cancerous tumor and the underlying pectoral muscle are not very frequent; for of 226 cancerous mammæ examined after extirpation, Schmidt found such adhesions only in 22 (9.7 per cent.). This may in some measure be due—as Volkmann has suggested—to the direction of the lymph current of the muscle being from the latter to the fascia, and not in the converse direction.

Stiles has lately devised a method for determining, without microscopical examination, whether the whole of the cancerous growth and glandular tissue has been removed or not. The breast is first freed from blood by immersion in running water; it is then submerged (whole or sliced) for about ten minutes in a quart of five-per-cent. aqueous solution of acidum nitricum, B. P., and then washed again for a few minutes, after which it is placed in undiluted methylated spirit. By this method the highly albuminous epithelial cells are converted into a dull, grayish-white, opaque substance, which can be readily distinguished from the more translucent stroma. From the arrangement of the opaque epithelial areas, their cancerous or noncancerous nature can generally be determined. In this way the relations of the neoplasm to the gland, its exact limits, and the mode and extent of its infiltrations can be definitely ascertained.

As the result of the extensive application of this method, Stiles, like Heidenhain, has found that the disease is very seldom completely extirpated by the ordinary operative proceedings hitherto in vogue. He has especially pointed out the facility with which the skin over cancerous growths becomes affected, owing to its connection with the ligamenta suspensoria of Cooper, and their contained glandular processes, lymphatics, etc., along which the disease readily spreads.

As previously mentioned, at a comparatively early stage of the disease there may frequently be found in the vicinity of the primary neoplasm small, really discontinuous, satellite nodules, which are the first signs of regional dissemination. These arise, as Langhans, Waldeyer, and others have shown, from cellular elements detached from the primary tumor, and conveyed to their new destination by the lymphatics or veins, or by their own spontaneous movements.

In mammary cancer the tendency to local dissemination is very marked. Török and Wittelshöfer, basing their observations on 366 post-mortem examinations, met with it in about 52 per cent. of all cases. They found obvious nodules in the skin in 10 per cent., in the paramammary fatty tissue in 8 per cent., in the pectoral muscles in 16 per cent., in the intercostals in 6 per cent., in the ribs in 8 per cent., in the sternum in 5 per cent., in the clavicle in 8 per cent., in the pleura and lungs in 6.8 per cent., in the pericardium in 0.54 per cent., and in the opposite breast in 9 per cent.

The skin is, of course, very much more frequently invaded than is implied by the above figures, which apply only to the discontinuous formation of obvious tubers, and not to its infiltration by the direct extension of the disease. In one or other of these ways, Gross found that the skin was involved in over 62 per cent. of all cases.

It is by no means rare for cancer of one breast to be followed after a time by outbreak of the disease in the other. This occurred in 8 of the 44 necropsies in my list, or in 18.1 per cent. According to Gross it is a late symptom, not supervening on the average until 29.8 months after the onset of the primary disease. Of 9 such cases under my observation, 4 were due to lymphatic dissemination, 3 to direct extension, 1 to metastasis, and 1 to multiple origin.

In certain rare cases of irregular lymphatic dissemination the disease may be conveyed to the large nerve cords of the axilla, to the upper end of the humerus, to the retrosternal lymph glands, thymus, etc. Under the latter circumstances cancer sometimes spreads to the sternum, causing an external prominence at the junction of its first and second segments. According to Key and Retzius, the lymph circulation of the nerves is entirely separate from that of the general lymph circulation; this may account for the rarity with which the disease disseminates in the large nerve trunks, notwithstanding their richness in lymphatics.

Local dissemination has an important bearing when the question of operation is under consideration, for it appears from the following considerations that the spread of the disease to the lymphatic glands and to the system generally is greatly favored by local dissemination. Thus, of 192 mammary cases with local dissemination, Török and Wittelshöfer found the lymphatic glands invaded in 52.6 per cent., and metastases in 72.9 per cent.; whereas of 174 cases free from local dissemination the lymphatic glands were affected in only 42.5 per cent., and there were metastases in but 45.4 per cent.

In structure, these local disseminative nodules are almost identical with the primary tumor whence they originate; and they constitute fresh centres of the disease, which progress precisely as the latter.

In the uterus, as the primary growth increases in size, it invades the musculature, and subsequently the parametrium. In the cervix the disease manifests marked tendency to spread downwards, forwards, and outwards, towards the anterior vaginal wall and the base of the bladder, rather than in other directions, probably owing to the greater freedom of the lymphatic channels along these lines; and the upper part of the vagina is almost always invaded. In the corpus the tendency of the disease is to spread towards the peritoneum; but it progresses slowly, the musculature often becoming greatly thickened, so that the uterus may acquire an enormous size.

At a comparatively early stage, there will usually be found in the vicinity of the primary neoplasm, or even at some distance from it, small satellite nodules, which are the first obvious signs of regional dissemination. Upon histological examination these are found to consist of solid plugs of cancer cells, vegetating within the lymphatic vessels, the intima of the latter taking no part in the morbid process. According to Seelig, these plugs arise from epithelial elements, detached from the primary neoplasm and conveyed to their new destination by the lymphatics, especially by the perivascular lymphatics. It is mainly through the spread of the disease from the latter to the adjacent blood-vessels that these are eventually implicated in a similar way.

It is generally believed that cancer of the uterus tends to remain localised longer than cancer of most other organs; but on this subject there has been much exaggeration. In fatal cases that have run their entire course, more or less local dissemination is of almost invariable occurrence. Leopold's researches show that, even at a comparatively early stage of the disease, too much reliance must not be placed on this alleged immunity from dissemination; for of 127 cancerous uteri extirpated per vaginam, he found dissemination in the parametrium in 68, or in 54 per cent.; the disease being limited to the uterus in the other 59 cases. Mackenrodt has arrived at similar conclusions. He found that the ablation of the disease had often been but incompletely effected; for, on microscopical examination of the apparently healthy tissues divided by the surgeon's knife, numerous cancerous foci were revealed.

Invasion of the parametrium causes diminution of the normal mobility of the uterus, and eventually its complete fixation. In cancer of the cervix, owing to this cause, the uterus is nearly always depressed as well as fixed, and thus the vagina appears to be shortened. It would be a mistake to infer, from what has been stated, that cervical cancers spread only in a downward and forward direction; for, in no inconsiderable proportion of cases, the disease extends backwards towards the rectum. Other localities in which dissemination is apt to occur are the ovaries, tubes, broad ligaments, pelvic peritoneum, great omentum, and adjacent intestines.

Cervical cancer may also spread upwards and invade the corpus; this need excite no surprise, when we recollect the freedom of the anastomoses between the lymphatics of the two segments of the uterus, and the facility with which retrograde lymph currents are set up.

A considerable number of cases of primary cancer of the cervix have now been recorded, in which cancerous foci were also found in the corpus, without there being any obvious alteration of the intervening parts. Seelig has pointed out, that the communication between the lymphatics of the cervix and those of the body, is very much freer through the numerous large branches within the musculature, than it is through the much smaller branches uniting the mucosa of the two uterine segments; and he believes that instances of multiple cancer, such as we are now discussing, are due to dissemination of the disease along these lines, rather than to multiple origin. In a few cases the primary outbreak has been in the corpus, and the secondary one in the cervix; most of these are probably also due to dissemination, but Winter and others think that some of them are caused by inoculation of the cervix through contact with the cancerous disease of the corpus or with *débris* given off from it.

As the primary growth extends, it gradually blends with the adjacent outlying nodules; and thus a diffused mass of cancerous infiltration results. In this way, when the inferior segment of the uterus is the part primarily affected, this structure, the anterior wall of the vagina, the base of the bladder, and adjacent parts are glued together, and the infiltration is apt to invade also the periurethral tissues; moreover, in a considerable proportion of cases it spreads backwards, involving the rectum and adjacent structures.

As the disease extends towards the base of the bladder it surrounds the lower ends of the ureters, compressing them and destroying their mobility. The precise spot at which this first happens probably is altogether outside the bladder, where the ureters lie close to the vaginal wall before they bend forward to perforate the base of the bladder; at any rate, this is what I infer from the not infrequent occurrence of hydronephrosis in the absence of any cancerous infiltration of the bladder. An impediment is thus offered to the outflow of urine, in consequence of which the ureter, together with the pelvis of the kidney and its calyces, becomes distended by the accumulating urine—hydronephrosis.

It sometimes happens that the cancerous tumor obstructs the ureters simply by compressing them, as in a case reported by Jourdan. The experiments of Lewin and Goldschmidt show the facility with which, even under normal conditions, reflux of urine from the bladder into the ureters may occur; while the least hindrance to the outflow causes it at once, when the bladder is full.

The purely mechanical effect of this hydrostatic compression on the kidney is to cause atrophic changes in the papillæ and pyramids, and eventually in other adjacent renal structures; but besides this, after a time, interstitial nephritis usually supervenes—indeed, according to Lancereaux, inflammatory changes in the kidney are of invariable occurrence in advanced cases.

Complete obstruction of the ureters is decidedly rare; hence the whole renal tissue is seldom destroyed. I have seen a case in which the cancerous disease, having invaded the wall of the ureter, spread upwards along it to the pelvis of the kidney; and another case in which the cancerous growth, having perforated the lower part of the ureter, grew upwards within it to the pelvis of the kidney.

It is highly exceptional for uterine cancers to run their entire course without inducing hydronephrosis, and the affection is nearly always bilateral.

The extension of ulceration to the base of the bladder brings with it a dangerous crop of complications, viz., perforation of the bladder, cystitis, ascending ureteritis, pyelonephrosis, suppurative pyelitis, and acute interstitial nephritis, with the occasional formation of miliary abscesses. In like manner the rectum may be perforated. Eventually the remains of the bladder, uterus, and rectum become converted into one large, ulcerated, cancerous cloaca; whence profuse putrid discharge issues, causing vaginitis and vulvitis, which sometimes assume a membranous character.

In most cases of uterine cancer the fatal issue is determined by some such intercurrent complications as the foregoing.

As the disease spreads towards the peritoneum localised adhesions are formed, matting the pelvic contents together, and so shutting off the advancing cancer from the general peritoneal cavity; but, in spite of this, general peritonitis not infrequently ensues, and in a certain proportion of cases fatal perforation. In like manner adhesions often arise between the diseased uterus and the great omentum. Adjacent loops of bowel—usually sigmoid, rectum, or ileum—may also be involved, giving rise to intestinal obstruction, or even to perforation.

The relative frequency of the occurrence of the above-mentioned lesions may be gauged from the following analysis of 78 post-mortem examinations on patients dead of uterine cancer, many of which were made by myself.

The *vagina* was extensively infiltrated in 72 cases, and in 6 cases it was scarcely at all invaded.

The *bladder* was infiltrated in 56 cases, and in 29 it was perforated as well.

There was extensive *renal disease* in every case: hydronephrosis was met with in 67 cases (5 being complicated with suppurative pyeloureteritis, 2 of which ended fatally by perforating into the peritoneal cavity); in 57 of these cases the disease was bilateral, and in 10 unilateral; in most of them there was concomitant nephritis; in 11 cases hydronephrosis was present, although the bladder was quite free from cancerous disease. There was evidence of acute cystitis in 15 cases.

The *rectum* was infiltrated in 19 cases, and in 10 it was perforated as well.

The *pelvic contents* were matted together by adhesions in 34 cases; and in 10 of these cases there were, as well, old peritoneal adhesions throughout the whole abdominal cavity.

In 13 cases the *pelvic peritoneum* was cancerous—Douglas' pouch in 7, general in 6, anterior cul-de-sac in 2 cases; 4 of these cases had perforated into the peritoneal sac, and so caused fatal peritonitis. In 2 cases intestinal obstruction had resulted from adhesions between the ileum and sigmoid flexure respectively; and in several other cases the intestines were adherent, as also was the great omentum.

The *ovaries* were invaded in 13 cases (both in 8, the left in 4, and the right in 2 cases).

In the *broad ligaments* there were cancerous deposits in 5 cases.

Kiwisch found the *tubes* cancerous in 18 out of 73 necropsies.

In operative procedures for uterine cancer, it is important to recollect the frequency with which the disease becomes disseminated in the ovaries, tubes, and broad ligaments. When the neoplasm originates from the fundus or its vicinity, dissemination along this track is of special frequency.

Pyometra was met with in 3 cases; *pyosalpinx* in 5 cases (double 4, single 1)—1 of which ruptured into the peritoneal sac; and *hydrosalpinx* in 2 cases.

Lymph-Gland Dissemination.

One of the earliest consequences of the development of a cancerous tumor is that the adjacent lymph glands become enlarged. This condition may be only transitory, as in the glandular enlargements occasionally seen in the course of most infectious diseases, in association with certain non-malignant tumors, and in the glands left behind after extirpation of a cancerous part. Such enlargements are usually ascribed to "irritation" or "chronic inflammation." Histological examination reveals nothing more than undue increase in number and size of the lymphoid cells, together with thickening of the fibrous reticulum and proliferation of its nuclei, as well as hyperplasia of the endothelia. These changes cause obstruction of the lymph sinuses, and consequent clogging of the circulation through the gland.

When associated with cancer, this glandular enlargement is usually followed, after a time, by the development in the affected glands of cancerous growths, similar in character and structure to the primary neoplasm. This indicates that the secondary growths are derivatives of the primary one. Yet it is exceptional to find any direct continuity between the two. Wherein, then, does the connection consist? We have seen that the lymph radicles communicate directly with the cancer alveoli. Hence detached cellular elements from the neoplasm may easily enter the lymphatics, and be carried by the lymph stream into the adjacent glands, just as happens with particles of coloring matter after tattooing. From the smallness of the lymph radicles, it may be inferred that such transported fragments must be exceedingly minute—probably a single cell or a small cellular group in most cases. That epithelial cells thus dissevered from their normal connections may still grow and multiply we know from the familiar process of skin grafting. Probably all cancer cells are capable of dissemination, but all are not capable of growing when disseminated. There are good grounds for believing that the majority of these "cancer emboli" perish and are absorbed, owing to the metabolic activity (phagocytosis) of the cells of the glands; and that only those with sufficient vitality to overcome this resistance originate dissemination tumors. Hence the lymph glands form a temporary barrier to the spread of the disease, and do not themselves usually become affected until a considerable time after the primary outbreak.

Gussenbauer's histological researches confirm this. He found traces of cancer cells disseminated in the glands of the neck, secondary to primary disease of the lip, in twenty-nine out of thirty-two consecutive cases, and doubtful evidence of it in the other three. Yet clinical experience proves that when the primary disease is extirpated without removal of the adjacent glands, in a considerable proportion of cases the latter do not originate recurrences. Similarly of Küster's one hundred and seventeen breast-cancer extirpations, in which the excised axillary glands were microscopically examined, in only two instances were they found perfectly free from any signs of cancerous dissemination; and of six cases of the same disease, with no enlargement of the axillary glands clinically appreciable, Gussenbauer nevertheless found—on histological examination after removal—evidence of dissemination in these glands in every case. But we know from clinical experience that after extirpation of cancerous breasts, without opening the axilla, recurrences in the axillary glands are proportionately much less frequent than this.*

We have thus arrived at the important conclusion that the outbreak of the disease in the lymphatic glands is due to grafts from the primary neoplasm arrested there, which subsequently develop in accordance with their inherent tendencies. This explains the great resemblance always noticeable between the primary and secondary growths, the significance of which it is impossible to ignore. Moxon has sagely insisted upon this. He says: "The first cancer which appears has a likeness to the part in which it appears, and the secondary cancers arising from it have the likeness of that first cancer; and those who doubt that they came from that first cancer must show us why they have that likeness." In this connection Waring's experiments are of interest, for they show that the cellular elements of the secondary, as well as those of the primary growths, in cancer of the pancreas and stomach, produce the same ferments, etc., as the normal secretory cells of these parts.

On examination of affected glands removed at an early stage of the disease, it can generally be made out that the new growth consists of but a few small, circumscribed foci, situated in the perifollicular lymph sinuses of the cortex or in their immediate vicinity—that is to say, in the course of the normal afferent lymph stream.

In a case of melanotic cancer of the breast, with secondary lesions in the axillary glands, the dark color of the cells enabled Billroth to follow the extension of the dissemination along the lymph sinuses; and his observations have since been confirmed and amplified by Zehnder. The latter describes the initial foci as increasing in size by continuous proliferation of their constituent cells, which soon assume the alveolar arrangement, just as in the development of the primary tumor in the breast. These cells are very rich in karyokinetic figures, and they can easily be distinguished from the cells (lymphoid) of the parenchyma of the gland, which show no signs of reproductive activity, and appear not to participate in the spread of the disease. Petrick has arrived at similar conclusions. Finally, by multiple staining, Gibbes has conclusively demonstrated the correctness of this interpretation. Large multinucleated cells, the so-called "giant cells of cancer," are also of frequent occurrence. As the cancerous grafts increase in size, the parenchymatous cells of the gland suffer atrophy, the blood-vessels of the stroma enlarge, and their endothelial and muscular coats thicken. The endothelial cells of the lymph vessels and glands show no visible alterations, and they evidently take no active part in the process. In its subsequent course the disease progresses precisely as the primary outbreak.

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* Of thirteen mammary cancers, with no appreciable enlargement of the axillary glands, for which the breast alone was removed, in three there was no return of the disease three years and upwards after the operation (Hildebrand).

Although the lymphatics connecting a cancerous tumor with the affected glands are usually free from disease, yet it occasionally happens that they are found distended with cancer cells. The so-called lymph cord, often to be felt passing from a mammary cancer to the axillary glands, is usually nothing more than the axillary tail of the mamma itself. The glands first affected are those that receive their lymph directly from the part of the organ involved by the primary neoplasm, and the subsequent spread of the disease from gland to gland corresponds to the course of the lymph stream; but it must be borne in mind that each infected gland constitutes a new centre of dissemination. In cancer we never meet with any general infection of the lymphatic system, such as is often observed in tubercle, syphilis, and other infectious diseases. This important fact, taken with the foregoing considerations, is an indication against the fancied resemblance traced by some pathologists between these diseases and cancer. Here it may be mentioned that malignant neoplasms have the property of reproducing their like by dissemination in the adjacent lymph glands, etc. The few instances in which it is alleged that non-malignant neoplasms (thyroid adenomata, uterine myomata, ovarian cystomata, etc.) have manifested similar properties are capable of being otherwise explained.

The comparative frequency of lymph-gland dissemination and the period at which it is most prone to supervene, vary according to the different localities in which the primary disease originates. In "rodent ulcer" any dissemination at all is almost unknown. Gliomata are malignant neoplasms that are said also never to disseminate, and it is certainly rare for the disease to spread in this way. In an infant two and one-fourth years old, with recurrent glioma retinæ, I have however seen dissemination in the dura mater and in the right deltoid muscle. These differences depend mainly upon the interaction of three variable factors: (1) the size and qualities of the cancer cells themselves, and their degree of cohesion; (2) the comparative richness or otherwise of the lymphatics in their vicinity, and the relation of the latter to the cancer elements; (3) the phagocytic properties of the invaded lymph glands.

Considering the great importance of this subject in connection with the treatment of mammary and uterine cancer, I have selected these forms of the disease as the most suitable for illustrating in detail the chief features of lymph-gland dissemination.

About a dozen lymphatic glands are normally to be found in the axilla, but in cases of cancer this number is often greatly exceeded. In a mammary-cancer patient operated on by Gross, fifty diseased glands were removed, which varied in size from a small shot to a large nut. I have seen several instances in which the number was nearly as great. This condition is no doubt due to morbid enlargement of the numerous small lymph-glandular structures normally present in the axillary fat, although ordinarily invisible to the naked eye. The number of glands usually affected is of course much less than this, but half a dozen or more are often obviously diseased; yet the resulting tumors seldom attain large size. When, however, only a few glands are involved, or but a single one, tumors larger than usual often ensue. Cancerous axillary glands generally remain discrete; but sometimes they blend together, forming a single, hard, irregular, nodular mass.

In most of our standard text-books the axillary glands are described as lying along the inner side of the axillary vessels. I need hardly remind any practical surgeon, that it is useless to seek for enlarged glands, secondary to disease of the breast, in this position. The axillary glands that, as a rule, first receive the lymphatics from the breast are those situated on the chest wall at the lower part of the inner side of the axilla, under the border of the pectoralis major muscle (pectoral glands). These are usually the first to be invaded in cases of cancer. It is well to remember that the axillary tail of the mamma lies close by them, and under certain circumstances it may easily be mistaken for an enlarged gland.

The remaining axillary glands are grouped as follows: (*a*) those along the inner side of the large vessels, which receive the lymphatics from the upper limb and are in free communication with the foregoing (brachial); (*b*) those of the posterior part of the axilla, deeply seated along the course of the subscapular vessels, which receive lymphatics from the back (subscapular); (*c*) a few small glands immediately below the clavicle (infraclavicular), between the pectoralis major and deltoid muscles, which receive branches from the arm and shoulder, and communicate above with the inferior cervical and below with the pectoral glands. There can be no doubt—as pointed out by Hyrtl and Reiffel—that some lymphatics from the mamma reach the glands at the upper part of the axilla, through Mohrenheim's space, without entering the pectoral group. These pass between the sternal and clavicular parts of the pectoralis major muscle, entering the axilla above the pectoralis minor, where they have often been found infiltrated in cases of mammary cancer. These various groups of glands communicate—directly or indirectly—with one another, so that all may eventually become diseased from a single morbid focus. Their efferent vessels ascend with the subclavian vein, and having formed one or more trunks terminate on the left side in the thoracic duct, and on the right side in the right lymphatic duct or subclavian vein. Next to the pectoral glands, those in the vicinity of the large blood-vessels and nerves are the ones chiefly affected in cancer of the breast—as far upwards as the clavicle, and sometimes even above this level.

When these glands are extensively involved, œdema of the upper extremity from pressure on the axillary vein may ensue; and at the same time there often is great pain from compression of the large nerve trunks. Should this condition pass on to gangrene, the suffering of the patient will be very great, for death is then approaching in one of its most horrible forms. It is for the relief of such cases that German surgeons have resorted to amputation at the shoulder-joint, etc. "Lymphatic œdema," from obstruction of the lymphatic circulation, is comparatively rare. In its extreme form, I have never seen an instance of it in connection with mammary cancer; but minor—more or less transitory—forms of lymphœdema I have several times seen. The disease rarely encroaches on the main arterial trunks; O'Connor has, however, reported an instance of dry gangrene of both upper extremities, owing to this cause: the patient, aged 56, was the subject of recurrent cancer in both breasts; the axillary and supraclavicular glands being invaded as well.

The lymphatics of the breast are extremely abundant. No other gland can compare with the mamma in this respect. Moreover, its lymphatics are relatively much more numerous than its blood-vessels, and their intercommunications are very free. Inasmuch as the spread of cancer and other diseases is effected mainly through their agency, accurate knowledge of their disposition is a matter of great practical importance. They consist chiefly of two sets: superficial ones derived from the skin, and deep ones from the gland. The superficial lymphatics are most abundant in the nipple and areola, where they form fine networks. From these a variable number of branches arise, which join the subareolar lymphatic plexus, towards which the deep lymphatics from the gland itself also converge. The lymphatics of the mammary gland are unequally distributed on its two surfaces, the anterior set being the larger and more numerous. Most of the large trunks that go to the axilla arise from these vessels. Each acinus, lobule, and lobe is surrounded by intercommunicating lymphatic anastomoses. The branches from these various sources converge towards the areola, beneath which their large trunks communicate freely, forming the subareolar plexus of Sappey. This plexus is the meeting-point of the chief mammary lymphatics. Hence cancerous neoplasms, originating in this part of the gland, are particularly apt to be attended by widespread acute local diffusion.

From this plexus two main trunks arise—one from its outer and one from its inner side—which course in the subcutaneous fat to the axilla. Each receives one or more branches from the upper and lower peripheral parts of the gland. Sometimes these peripheral branches join the axillary glands independently. In the axilla it is rare to find more than two or three large lymphatic trunks. The above description is mainly after Sappey, but I think this distinguished anatomist is in error, in maintaining that all the lymph from the breast necessarily passes through the subareolar plexus. There are other lymphatics proceeding from the breast besides those described by him. Some accompany the blood-vessels (perivascular). These consist merely of a layer of endothelial cells lining the connective sheaths of the vessels they accompany. Numerous other efferent branches, as Langhans has shown, pass from the posterior part of the breast into the loose retromammary connective tissue, whence they proceed to the axilla without ever entering the subareolar plexus. Through these branches cancer frequently disseminates. Some lymphatics, from the deep aspect of the breast, also enter the chest through the pectoral and intercostal muscles, and so come into close relationship with the pleura. In fact, through the medium of numerous arterial, venous, and lymphatic vessels, the pleuræ and mammæ are closely related. Hence the frequent association of pleurisy and pleural effusions with cancerous and other affections of the mammæ; hence also in certain intrathoracic diseases the mammæ may be secondarily involved. Lymphatics from the upper part of the mamma sometimes pass directly to the infraclavicular and inferior cervical glands. Others, from its sternal part, pass through the second, third, fourth, and fifth intercostal spaces, to the anterior mediastinal (retrosternal) glands, where they communicate with the anterior intercostal, internal and external mammary branches. Waldeyer has shown that the retrosternal fatty tissue and the thymus remains are remarkably rich in lymphadenoid structures. It is strange that cancerous dissemination does not affect these glands more frequently than it appears to do. Török and Wittelshöfer found them diseased in only 6.5 per cent. of all their necropsies. In this connection, it is of interest to recall the fact that cancer originates in the sternal segment of the gland much less frequently than in any other part.

The paramammary lymphatics communicate on the one hand with circumferential mammary branches—from both the superficial and deep aspects of the gland—and on the other with the subcutaneous thoracic lymphatics. Through these channels the lymph systems of both breasts communicate indirectly. Thus may be explained those rare instances in which cancer of one breast has caused disease of the glands in both axillæ (Scarpa, Cooper, Moore, etc.), and others in which cancer of the sternal segment of one breast has induced secondary disease in the glands of the opposite axilla (Volkmann). In a case mentioned by Moore, cancer of the left breast disseminated not only in the glands of the left axilla and groin, but also in those of the opposite axilla.*

It is a matter of considerable practical importance to determine how soon after detection of the primary neoplasm the axillary lymph glands become diseased. According to Fink, this happens as early as from the sixth to the twelfth month; and after the thirteenth month they are invariably invaded. Winiwarter estimated the period at from fourteen to eighteen months. Gross gives the average as 14.7 months. These are but clinical data, which, of course, do not enable us to affirm that the glands are free from disease for the whole period of apparent immunity. In forty-three of Küster's cases, with no clinically appreciable disease of the glands, signs of cancerous dissemination were nevertheless found in them on histological examination after removal. On the other hand, Poulsen reports twenty-one cases in which the mamma was removed for cancer—the axilla not being touched—in which the patients afterward remained free from recurrence for three years or more, although in several of them the disease had existed for long periods prior to the operation. Schmidt and others have met with similar cases; hence there are evidently exceptions to the rule of early gland dissemination.

In some very rare instances glandular implication is so rapid that it appears to coincide with or even to antedate the primary disease. In others it may be delayed for several years—for ten years or even more—or it may never occur at all. Certain scirrhous cancers may undoubtedly run their entire course, causing systemic dissemination and death, without the adjacent lymph glands ever being implicated. Hence the absence of lymph-gland disease is no absolute guarantee against general systemic dissemination, which in these cases evidently takes place through the blood-vessels. According to my experience, such occurrences are most exceptional. I have met with but a single instance of the kind in forty-four consecutive necropsies on patients who had died of mammary cancer, there being metastases in twenty-eight.

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* The connections between the axillary and groin lymphatics are well shown in one of Sappey's plates ("Des Vaisseaux Lymphatiques," Paris).

According to Gross, metastases occur without any antecedent lymph-gland dissemination in about one in seven of all cases. This estimate appears to me too high, probably because many operative cases have been included. Török and Wittelshöfer's figures, which are much higher still, err also from this cause.

An idea of the frequency of lymph-gland dissemination may be gathered from the following figures:

Of 118 cases of primary cancer of the breast consecutively under my observation, there was obvious glandular disease—when the patients were first seen—in 86, or in 73 per cent. In all of these cases the axillary glands of the same side as the disease were affected, with the supraclavicular as well in 5 cases, the infraclavicular in 2, and the glands of the opposite axilla in 2—both breasts being involved in these cases.

Gross gives the proportion of cases of gland dissemination under like circumstances as 68 per cent., those of the axilla being diseased in all, the supraclavicular in 5.4 per cent., and the infraclavicular in 1.3 per cent.

Turning now to the post-mortem evidence, what I have found in the cases under my own observation is that of 44 consecutive necropsies, there was lymph-gland dissemination in 40, or in 90.9 per cent.; the axillary glands were affected in all, with both the supra- and infraclavicular ones in 5 cases, the supraclavicular alone in 2, the infraclavicular alone in 4, and those of the opposite axilla in 10 cases (in 7 of these both breasts were cancerous).

In three of the four cases in my list free from lymph-gland disease, cancerous axillary glands had just previously been removed by operation.

From this it follows that dissemination in the adjacent axillary glands is sooner or later an almost invariable concomitant of acinous (scirrhous) cancer of the breast; the cases that run their course without it are of great rarity.

Should any one oppose to this conclusion Török and Wittelshöfer's analysis of 366 necropsies, in which the axillary glands were found invaded in only 175, or 48 per cent., my answer is that these statistics are useless for determining the point under consideration, because of the large number of operation cases they include, in which the affected lymph glands had recently been removed.

It is commonly stated that the progress of the disease is much slower, and the total duration of life much longer, in cases in which lymph-gland dissemination is long delayed, than in those in which the glands are attacked at an early period of the disease. I am not aware of any statistical evidence that can be adduced in support of this belief, but my impression is that it is well founded.

It is, however, clearly shown by statistics that lymph-gland affection is an important factor in determining the results attained by operations for the removal of the disease.

Thus, according to Winiwarter, after amputation of the breast for the primary disease, with removal of affected axillary glands, the subsequent duration of life averaged 13 months, the total duration being 29 months; whereas when the breast was amputated, without removal of axillary glands—none being obviously affected—the subsequent duration of life averaged 22 months, the total duration being 50 months.

Gross' statistics are equally conclusive. Thus of 136 cases of extirpation of the breast, in 93 diseased glands were removed; the total duration of life averaged 39.3 months, and local recurrence ensued on the average in 1.9 months; whereas in 43 cases free from gland dissemination, the average duration of life was 52.7 months, and the average period of recurrence was 8 months. The latter, therefore, lived 13.4 months longer than the former, and when recurrence followed, it appeared 6.1 months later.

The same author has shown that the proportion of cures after operation is 5.1 per cent. greater when the axillary glands are free from disease, than it is when they are obviously affected. Poulsen's testimony is to the same effect, for 22 per cent. of his operated cases (in most of which the glands were not obviously affected) were well for three years or more after extirpation; whereas of 43 operated cases (in which the glands were demonstrably involved), only 4 (9.3 per cent.) were well at the end of that period.

These data indicate that the best time for extirpating the disease is before the glands have become obviously involved.

Recent researches (Poirier, Sappey) show that the uterus is exceedingly rich in lymphatics, whose numerous branches communicate freely with one another, as well as with offsets from adjacent organs. Owing to the inefficiency of the valvular apparatus, lymph currents are often established in directions other than the normal. Hence the whole system may usually be injected by inserting the syringe into almost any part of the organ; hence also, in cancer, we need not be surprised to meet with dissemination in localities not directly in the course of the normal lymph stream.

The mucosa is permeated throughout with lymphatic channels; but the precise manner in which they originate and their exact relation to the utricular glands have not yet been definitively determined. Leopold regards the stroma of the mucosa as consisting of an intercommunicating system of lymph spaces, in which the glands, etc., are embedded; the small round-celled interglandular elements he considers to be lymphocytes.

From the mucosa efferent branches pass to the musculature, which encloses an immense number of large clefts and sinuses, freely communicating.

From this source branches are given off in great numbers, which emerge on the surface of the uterus, beneath the peritoneum, where they ramify and anastomose in the subperitoneal connective tissue. These vessels communicate freely with the subendothelial lymphatic plexuses of the peritoneum.

The lymphatics of the corpus, cervix, and portio communicate by numerous anastomoses, which are especially free within the musculature and along each lateral border of the uterus; while inferiorly they are joined by vaginal offsets.

The efferent branches from the corpus converge to form two large trunks on each side, which then enter the upper part of the broad ligament with the uteroovarian blood-vessels; they pass thence beneath the ovary to the upper border of the broad ligament, where they are reinforced by numerous branches from the ovary and tube, which anastomose with them higher up; thence they follow the course of the utero ovarian blood-vessels to their termination in the lumbar glands.

The latter consist of median and lateral chaplets of ganglia, with numerous intercommunicating branches, which completely surround the aorta and vena cava. They extend from the receptaculum chyli above, to the angle of bifurcation of the common iliac artery below, where they become continuous with the iliac glands. The lowest lumbar gland, which receives lymph directly from the corpus uteri, is situated on a level with the inferior extremity of the kidney; those next higher up get ovarian as well as uterine lymph. Cancerous enlargement of these glands, by compressing the aorta or vena cava, may cause interference with the circulation through these vessels.

Some lymphatics from the corpus uteri go with the round ligament to glands in the groin, as described long ago by Mascagni.

This explains one mode of dissemination of uterine cancer in these glands.

The adhesions, so common between the uterus and adjacent parts, are rich in lymphatics, which communicate with those of the uterine peritoneum.

Efferent branches from the cervix emerge at numerous points of its surface, and anastomose in the periuterine tissue, gradually forming larger and larger vessels; which, after being joined by several offsets from the portio and upper part of the vagina, converge to form two or three large trunks on each side of the cervix. These pass transversely outwards, with the uterine blood-vessels, along the inferior border of the broad ligament, towards the lateral wall of the pelvis; thence they proceed upwards and backwards to the upper ganglia of the iliopelvic glands.

The latter are a continuation downwards of the lumbar chain. Their highest ganglia are situated in the angle of bifurcation of the common iliac artery in close proximity to the external iliac vein, either of which vessels may be compressed by their enlargement. These ganglia are on a level with the upper part of the pelvis in the vicinity of the sacro-iliac synchondrosis. Thence communicating branches dip into the pelvis, whence the chain is continued downwards, in front of the internal iliac (hypogastric) artery on each side. It is the three upper glands of this series that, according to Poirier, receive the cervical lymphatics; and when enlarged they can be felt, per vaginam or per rectum, by deep palpation directed upwards and outwards, close to the lateral borders of the uterus.

The next succeeding gland of the series is situated over the great sacrosciatic foramen, in close proximity to the great sciatic nerve, which may be compressed by its enlargement; under these circumstances it can readily be felt on digital examination per rectum. Poirier describes these glands as receiving their lymph from the upper and middle parts of the vagina; but, according to Cruveilhier, these are the glands usually affected in cancer of the cervix uteri, and they are often the only ones implicated.

A continuous chain of ganglia extends from the iliolumbar series along the iliac blood-vessels to the crural canal, and by this route also the disease may reach the inguinal glands. The latter glands may also be directly affected when the disease reaches the anterior part of the vagina.

In the vicinity of the obturator foramen (Le Bec) and in the subpubic region one or more ganglia may occasionally be found which communicate with the foregoing, and in cases of uterine cancer these may exceptionally be indirectly infected.

Although a considerable number of uterine cancers run their entire course without causing any obvious dissemination in the adjacent lymph glands, yet it would be a mistake to suppose that lymph-gland dissemination is rare in uterine cancer; for, as a matter of fact, the adjacent glands are invaded in the great majority of post-mortem cases. Thus of my 78 necropsies, lesions of this kind were noted in 56, or in nearly 72 per cent. In 28 per cent., however, there was no obvious glandular affection. In mammary cancer, under like circumstances, as I have previously pointed out, lymph-gland dissemination is of almost invariable occurrence. Hence it is evident that this form of dissemination is of less frequent occurrence in uterine than in mammary cancer.

Several glands are usually involved. The first to be affected are those that receive their lymph directly from the part of the organ invaded by the primary disease, and the subsequent spread of the disease from gland to gland corresponds to the course of the lymph stream; but it must be borne in mind that each infected gland constitutes a fresh centre of dissemination.

These secondary growths are similar in structure and character to the primary neoplasm, and it seems certain that they owe their origin to the latter, through the agency of detached cellular fragments carried off by the lymphatics.

In uterine cancer the glands of the iliopelvic group are more frequently invaded than any others; there was dissemination in these glands in 44 of my cases, or in 56 per cent., and in 20 of them the pelvic glands alone were involved.

In a case of uterine cancer reported by Chapuis, owing to compression of the right internal iliac artery by a cancerous gland and consequent thrombosis of the common iliacs, dry gangrene of both lower limbs set in. In 7 of Lebert's 45 uterine-cancer necropsies, œdema of one or both lower limbs was met with, owing to cancerous glands pressing on the iliac veins. Lymphœdema, owing to obstruction of the lymph circulation, is of rare occurrence.

It is very exceptional to find only the lumbar glands affected; my list contains only two instances of this kind, but these glands are often involved by upward extension of the disease from the iliopelvic group, as in 24 of my cases.

There was dissemination in the inguinal, as well as in the iliopelvic glands, in 6 cases (both sides 4, right side 2); and in 3 other cases the mesenteric ganglia were also invaded. The disease has even been known to have involved as well the posterior mediastinal glands and the receptaculum chyli.

Troisier and others have lately called attention to some remarkable lymph-glandular affections (*adénopathies externes à distance*) that occasionally arise in the course of certain cancers, especially those that are intraabdominal. In this condition some of the superficial glands at a distance from the primary disease become enlarged, without any of the intervening structures necessarily being affected. The glands usually thus affected are those of the left supraclavicular region; but quite exceptionally the right supraclavicular, inguinal, axillary, or epitrochlear glands may be involved. Of 37 cases tabulated by Rousseau, in 29 the left supraclavicular glands were the ones affected, in 4 the right supraclavicular glands, and in 4 those of both these regions.

In the great majority of these cases we have to do with cancerous dissemination; but I have witnessed retrocession, and so has Girode. At first only a single gland is usually involved, then others of the group become affected, and these agglomerate. Pressure symptoms are comparatively rare, but I have seen an instance. It is usually a late symptom, and this probably accounts for the absence of ulceration and suppuration. Many cases have been noted in connection with cancer of the uterus, but in most cases the stomach is the seat of the primary disease. It seems probable that this curious pathological condition, is due to regurgitation of lymph—charged with cancer cells—from the thoracic duct into the adjacent cervical glands; which lymph—in the case of uterine cancer—is presumably conveyed to the thoracic duct by lymphatics derived from infiltrated lumbar glands. The presence of cancerous thrombi within the thoracic duct, in cases of uterine cancer, has actually been demonstrated by Cruveilhier and others. Though usually a late symptom, instances are on record in which this adenopathy has supervened at least two years before death. I need hardly insist on the importance of this manifestation as a contraindication to operation, and as an element in the diagnosis of obscure intraabdominal disease. It should be borne in mind, however, that tubercle, syphilis, and a few other morbid conditions may occasionally produce somewhat similar adenopathies; moreover, this affection must not be confounded with the *pseudo-lipôme sus-claviculaire* of Verneuil, which is simply an overgrowth of the fibrofatty tissue of the supraclavicular fossa—both sides being usually affected; those most liable being middle-aged women otherwise in good health.

In a certain proportion of these cancerous glands, the disease is complicated by the supervention of inflammation and suppuration; owing, as Zahn and others have shown, to their inoculation with pyogenic microbes, detached from the primary neoplasm with the original "cancer emboli."

As evidence of the rarity of dissemination in the adjacent lymph glands in the early stage of the disease, reference may be made to the fact that, in extirpating cancerous uteri, surgeons have seldom met with infiltrated glands; moreover, after extirpation, glandular recurrence is decidedly rare.

General Dissemination.

The appearance of cancerous growths in various parts of the body, remote from the primary disease and its derivatives (so-called *metastases*), to which allusion has already been made, is one of the most striking features of the disease. It is remarkable that the cancers of every locality have their own special modes of dissemination, and even the various forms of the disease in particular organs manifest differences in this respect.

The female breast is one of those parts of the body in which the tendency to dissemination is very great.

Growths of this kind are met with in considerably more than one-half (61 per cent.) of all fatal cases of breast cancer.

Of 44 consecutive necropsies under my observation, systemic dissemination growths were found in 28, or in 63.1 per cent.; and of Török and Wittelshöfer's 366 necropsies they were met with in 215, or in 58 per cent. The percentage figures would be much higher but for the fact that in all the foregoing estimates very many cases, which terminated fatally shortly after operation, have been included. Ten of the 44 necropsies in my list were of this nature. Of the remaining 34 necropsies, in which death ensued in the natural course of the disease, there were metastases in 25, or in 73.5 per cent.

Statements vary as to the precise date of onset of general dissemination, but there is universal agreement that it is not until a comparatively late period of the disease—generally some two or three years after the initial outbreak, and about fifteen months after invasion of the lymphatic glands. Winiwarter, Sprengel, and Fink estimate it at twenty-five months, Henry at thirty, and Oldekop at thirty-eight months. As a rule, the slower the progress of the primary disease, the later metastases appear. Occasionally they form during the first few months, and at other times not until after the lapse of several years—even ten years or more. Schmidt has lately reported a case in which a woman died of cancer of the liver and lungs seven years after extirpation of the breast for the primary disease, of which there was no local recurrence.

According to Gross, out of 100 metastases 24 form within the first year, 3 in from 13 to 18 months, 18 in from 19 to 24 months, 27 in from 25 to 36 months, and 28 after 3 years. The average duration of life after the first appearance of metastases is, according to my estimate, about two years. Growths of this kind may exist for a long time in important organs, such as the liver, lungs, brain, etc., without causing any obvious functional disturbance.

In the *ensemble* of their characters—histological and otherwise—metastatic cancers closely resemble the primary neoplasm. They differ from the latter, however, in that they are usually multiple, and spring up in several different localities. Occasionally the number of metastases is very small, and in rare instances there may be only a single one. In soft, vascular organs like the liver, these growths often attain immense size; but in other parts they are commonly of moderate dimensions. Usually they present as small, hard, nodular, flattened, or discoidal masses, which soon become cupped or umbilicated, owing to contraction of the older parts of the growths. Occasionally they take the form of diffuse infiltrations, especially in the pleura and bones.

The sequence of their development and the combinations of organs invaded are difficult to explain. The deep parts of the body are much more frequently invaded than the superficial, but the order of eruption in most individual internal organs is just the converse of this.

I have seen it stated by good authorities, that metastases invariably affect both of paired organs, but I have convinced myself by repeated observations that it is often not so: both are usually affected, but often only one.

Sometimes these growths are exceedingly numerous and widely spread throughout the body, as in Velpeau's remarkable case of mammary cancer, in which hundreds of them were found distributed throughout the general connective tissue, lungs, liver, bones, muscles, heart, stomach, duodenum, small intestines, pancreas, kidneys, gall-bladder, vena cava, peritoneum, dura mater, and thyroid gland.

Similar cases have lately been recorded by Bramwell and Kantorowicz.

The following analysis gives a good idea of the relative frequency with which the various parts are affected in mammary cancer.

Of 44 consecutive necropsies, many of them made by myself, the seats of metastases were—

Liver	in 20 cases.	Gastrohepatic omental glands	in 1 case.
Lungs (B. 5, L. 2, R. 1)	“ 8 “	Vertebræ (lower dorsal and upper lumbar)	in 1 “
Pleura (B. 5, L. 1)	“ 6 “	Peritoneum	“ 1 “
Femur (B. 2, R. 1, L. 1)	“ 4 “	Uterus	“ 1 “
Retroperitoneal glands	“ 3 “	Ovary (L.)	“ 1 “
Bronchial glands	“ 2 “		

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Humerus (R. 1, L. 1)	in 2 cases.	Tibia (R.)	in 1 case.
Kidneys (B. 2)	" 2 "	Ribs (B.)	" 1 "
Suprarenals (B. 1, L. 1)	" 2 "	Spleen	" 1 "
Pancreas	" 2 "	Duodenum	" 1 "
Mesenteric and omental glands	in 1 case.	Mamma (of opposite side)	" 1 "

This analysis shows that metastases are of much more frequent occurrence in some parts of the body than in others.

The liver, lungs, pleuræ, and bones are their seats of predilection; while they are very rarely found in the lips, tongue, mouth, pharynx, œsophagus, small intestine, skin, mucous membrane, peripheral nerves, ligaments, tendons, prostate, urethra, bladder, pelvis, clitoris, vagina, lacrymal gland, parotid and other salivary glands, eye, ear, nose, thyroid, vermiform appendix, spinal cord, heart, muscles, nerves, stomach, uterus, mamma, etc. The only parts really quite exempt are non-vascular structures like cartilage, cornea, etc. Schapter has recently reported a case in which cancer of the lung disseminated in a uterine myofibroma.

Careful examination of the facts show that, strictly speaking, the mutual local exclusiveness between primary and secondary cancers, announced by Virchow, does not exist; nevertheless it is undoubtedly true that parts specially prone to originate the disease, *i.e.*, tongue, lip, skin, mouth, œsophagus, uterus, breast, stomach, etc., are seldom the seats of secondary outbreaks.

The *liver* is the organ most frequently affected with metastases in mammary cancer. My analysis shows this in a striking manner; but it would have been otherwise had I not carefully separated the true pulmonary metastases from those cases (twelve altogether), in which the lungs were invaded by direct extension of the primary disease or by its local dissemination. The discrepancy between my analysis and those statistics which place the lungs and pleuræ at the head of the list, is evidently due to this cause.

Dissemination in the liver rarely gives rise to marked symptoms, and jaundice is seldom thus caused; nodular enlargement of the organ is its commonest physical sign. Occasionally there is retraction of the umbilicus. In certain cases there may be no hepatic enlargement.

In mammary cancer, as I have previously mentioned, the ribs, sternum, and occasionally the clavicle may become cancerous through direct extension of the primary disease or through its local dissemination.

In addition to this, however, certain *bones* are very prone to metastases; thus of 533 mammary-cancer necropsies tabulated by me, there were metastases in the cranial bones in 36, vertebræ in 11, innominate in 9, femur in 8, humerus in 8, ribs in 4, tibia in 1, and in a bone not otherwise specified in 1.

Of 44 necropsies within my own experience, the femur was invaded in 4 cases, the humerus in 2, the vertebræ, ribs, and tibia each in 1 case.

The absence of metastases in the cranial bones in the latter group of necropsies is probably due to the fact, that the cranium was seldom opened, unless signs of intracranial disease had been noticed during life; whereas in most of the former series the cranium was opened as a matter of routine. It may be inferred from the discrepancy thus revealed, that intracranial metastases frequently exist without giving rise to any obvious symptoms. Of 40 intracranial metastases noted by Török and Wittelshöfer, the parts affected were: dura mater in 25 cases, cerebrum in 22, cerebellum in 13, pia mater in 3, and pineal body in 2 cases. Such lesions are generally single, but they may exceptionally be multiple. Cruveilhier reports having found over a hundred separate nodules in the diploë of a woman who had died of breast cancer.

Metastases in the *vertebræ* almost invariably originate in the bodies; usually several adjacent bones are affected, and in most cases the disease is situated in the lower dorsal or upper lumbar regions. As the growths progress they may cause excruciating pain, and eventually kyphosis or angular curvature, and sometimes paraplegia.

When cancer disseminates in the bones, several are usually involved, but quite exceptionally only one. Moreover, it is rare for disseminative lesions to be limited solely to the osseous system.

Of the long bones, metastases are commonest in the *femur* and *humerus*; both sides being generally affected, but often only one.

As an instance of widespread dissemination of this kind, mention may be made of a case I once saw in which, several years after amputation of the left breast for primary cancer, recurrence took place in the mammary region; and metastases subsequently formed in the liver, spleen, retroperitoneal glands, as well as in the following bones (all of which fractured spontaneously)—both humeri, right clavicle, third, fourth, and fifth right metacarpals, and the left femur. In this case the osseous growths were circumscribed.

In the femur, metastases generally originate in the medulla, at about the middle of its upper half; and in the humerus at the junction of its upper and middle thirds. As the growths increase, they cause "pressure atrophy" of the cortex, and so eventually spontaneous fractures. Until this happens, metastases in these bones seldom give rise to symptoms, other than quasi rheumatic pains. In making post-mortem examinations, I have several times found secondary growths in these bones, the presence of which had never been so much as suspected during life.

I have often noticed around growing endosteal cancers, a more or less extensive zone of decalcified osseous tissue; this preparatory softening of the adjacent bone no doubt accounts for the ease and rapidity with which these growths progress, notwithstanding the apparently unyielding nature of their surroundings. Fractures due to metastases generally excite a great deal of swelling, and they are followed by free formation of callus, so that firm union is sometimes attained.

There can be no doubt that dissemination in the osseous system occurs very much more frequently in connection with cancer of the breast than with cancer of any other part of the body. I have, however, met with metastases in the right tibia, secondary to cancer of the cervix uteri; and in the seventh and eight dorsal vertebræ (causing paraplegia), secondary to cancer of the lower part of the rectum; moreover, I know of instances of the dissemination of cancer of the cervix uteri in the left femur, in the upper part of the right humerus, and in the ribs. Instances of the dissemination of cylinder-celled cancer of the rectum in the right humerus, and of the same variety of cancer of the stomach in the right humerus, have also been recorded.

I have seen several instances in which elderly women, with mammary cancer, have sustained—in consequence of some trivial accident—spontaneous fracture of the upper extremity of the femur. Usually such cases have been mistaken for ordinary senile intracapsular fracture, until after a time the presence of mammary cancer has been discovered. *Spontaneous fractures of the upper part of the femur in emaciated, sallow, elderly women should always be regarded as suspicious of mammary cancer.*

On *à priori* grounds, there seems to be no reason why cancer of one breast should not cause, by systemic dissemination, secondary disease in the *opposite breast;* and of this condition I have seen at least one instance.

Metastases in the breast, secondary to cancer elsewhere than in the mamma, are by no means unknown. I have seen instances of this kind in which the primary disease was in the uterus, ovary, rectum, and peritoneum.

Gross' statistics show metastases in the *ovaries* in 8 per cent. of all breast-cancer necropsies. Of Nunn's and my 167 necropsies, ovarian dissemination was met with in 8 cases, or in 4.8 per cent. In 4 of these cases both ovaries were affected, and in 4 only one. Coupland has met with a case in which both breasts and ovaries were cancerous.

Instances of metastases in the iris and choroid, secondary to mammary cancer, have been reported by Legrange, Abelsdorff, and others, but such occurrences are of great rarity; so also is dissemination in the peripheral nerves, of which Cruveilhier has related a case, the portio dura being affected, in the form of nodular thickenings of the neurilemma.

There can be no doubt that the uterus is one of those organs in which the liability of cancer to disseminate to distant parts of the body is not very great.

I have met with lesions of this kind in about 20 per cent. of the fatal cases that had run their entire course; whereas I have found that dissemination had taken place—under like circumstances—in 73 per cent. of the cases of mammary cancer.

The probable explanation of this difference is that uterine-cancer patients are commonly cut off by fatal intercurrent complications before the cancerous disease has had time to mature, for this form of dissemination seldom sets in until a comparatively late stage of the disease.

The following analysis gives a good idea of the relative frequency with which the various localities are affected in cancer of the cervix uteri. Of 79 necropsies, I found that dissemination had taken place in 16, or in 20.2 per cent.

The seats of the disease were:

Lungs (both 6, right 1)	in	7	cases.
Liver	"	7	"
Peritoneum and omentum	"	4	"
Pleura (both 1, right 1)	"	2	"
Skin of chest and abdomen	"	1	case.
Tibia (right) and innominate bone (right)	"	1	"
Heart	"	1	"
Kidney (left)	"	1	"
Ureter (left)	"	1	"
Bronchial glands	"	1	"
Tibia (right) and innominate (right)	"	1	"

Dissemination in the bones is decidedly rare in uterine cancer; but, in addition to the above-mentioned case, I know of several others. The following case, in which secondary cancer of the humerus was mistaken for primary sarcoma of that bone, for which the limb was amputated at the shoulder-joint, presents so many remarkable features that it is well worth recording here.

The patient, aged 52, was admitted into University College Hospital on account of painful swelling at the upper part of her right arm, of two months' duration, she complained also of loss of power in the part, which began to weaken about a year ago. On examination there was found great enlargement of the upper end of the humerus, which extended as far down as the insertion of the deltoid. The overlying skin was reddened, and the subcutaneous veins were much enlarged. There was great loss of power in the limb, and constant "gnawing" pain was experienced, which extended to the elbow. Passive movements at the shoulder-joint could be effected, but they caused much pain. There was a family history of phthisis, and a sister had died of internal cancer. Her previous health had never been good. The swelling was aspirated, but only some blood and fatty matter came away. Under these circumstances it was resolved to amputate at the shoulder-joint. During manipulation, prior to operation, the bone fractured through the surgical neck. The part was removed by cutting the deltoid flap by dissection, and the internal flap by transfixion, with antiseptic precautions. The upper part of the humerus, as far down as the insertion of the deltoid, was found to be involved by a malignant growth; but the cartilage of the head was intact. The wound healed quickly; but the patient's health, nevertheless, progressively deteriorated, and she died about seven months after the operation. Some time afterwards it was discovered that she was suffering from ulcerated cancer of the cervix uteri, to which the cancerous tumor of the humerus was evidently secondary. Histologically examined, the latter growth consisted of fibrous stroma containing numerous small spaces, for the most part lined by but a single layer of short columnar cells; but some of the spaces were filled with spheroidal cells. The appearances were similar to those often met with in cancer of the cervix uteri.

Cancer of the breast is much more prone to disseminate in the *uterus* than uterine cancer is to disseminate in the mammæ. The massed statistics of Gross show dissemination in the uterus in 5.2 per cent. of all breast-cancer necropsies.

Metastases in the uterus secondary to mammary cancer, almost invariably affect the body of the organ, generally its peritoneal surface. In a case under my observation, several nodules were found in this situation, as well as in both pleuræ, the right femur, and the right humerus. In very exceptional cases, however, we do find dissemination in the cervix uteri secondary to mammary cancer; under these circumstances the uterine lesion begins as a nodule.

The following is a brief account of a case in which cancer of the cervix uteri disseminated in the left breast:

The patient, a married woman aged 49, the mother of one child. One and three-quarter years ago she first became subject to sanious vaginal discharges, and shortly afterwards flooding set in. She had since been subject to return of the latter every two or three months. Eight months ago the cancerous cervix was amputated. She was relieved for two months, when the old symptoms returned. Four months ago she first noticed a lump in her left breast, the size of a hazelnut; and two months later a small nodule appeared in the skin over the upper part of the sternum. When first seen by me she had a profuse saniopuriform vaginal discharge, and the portio vaginalis uteri was replaced by a hard, nodular, ulcerated surface, with infiltration of the adjacent parts of the bladder, vagina, and rectum. She complained of pain in the sacral and genital regions, and of difficult and painful defecation. At the lower and axillary part of her left breast was a hard, flattened nodule, the size of half a walnut, adherent to the overlying skin, but movable on the subjacent parts; the nipple was normal, and the axillary glands were not obviously affected. In the skin over the left edge of the sternum, level with the second costal cartilage, was a hard nodule the size of a pea. She died of asthenia six months later, and there was no necropsy.

By far the most feasible explanation known to me of the phenomena of systemic dissemination is that furnished by the "embolic theory." This implies that the germs whence metastases arise are proliferous cells, detached from the primary neoplasm or its derivatives, and carried off by the blood stream. These, by their continuous proliferation, directly originate the secondary growths; so that the first cancer is the parent of all that form after it. The conception of metastases, as due to specific virus (blastema, etc.) dissolved in the blood, belongs to the old humoral pathology and now finds no support except with those who would revive the old doctrine in connection with the microbe theory. Agreeably with this conclusion, metastases are never found in non-vascular structures, like cartilage and cornea; which are impermeable to cells, but not to fluids.

Friedreich's case of cancerous dissemination in the skin over the left knee of a fœtus—whose mother died during pregnancy with cancer of the liver and multiple disseminative nodules in the uterus, mammæ, bones, intestines, etc.—much relied upon by the advocates of infection by the fluids, as supporting their theory, can easily be accounted for by the embolic theory. We know from Porak's researches that foreign substances may pass through the placenta, although as a rule there is no mixing of fœtal and maternal blood. The permeability of the placenta to microbes has also been demonstrated. Hence we may infer that young cancer cells, which often are exceedingly minute, may also pass through the placenta. Lebert has reported a case, which evidently belongs here, of intraabdominal cancer in a four-months' fœtus, whose mother died of general carcinosis.

Many observations indicate that cancer cells enter the blood stream directly through the blood-vessels—especially the small veins—as well as indirectly through the lymphatics. In the latter instance, cancer cells taken up by the lymphatics, and not arrested by the glands, are carried on with the lymph stream into the large lymph trunks. Thus, Astley Cooper, Andral, and others have found free "cancer emboli" in the thoracic duct and in the large lymphatic trunks of this locality; and these vessels have often been found plugged with cancerous growth (Unger, Schramm, etc.). Under the latter circumstance chylous ascites is occasionally met with.

The occurrence of general dissemination, without any lymph-gland affection, shows clearly that cancer cells may enter the blood otherwise than through the lymphatics; and my own belief is that metastases frequently originate in this way, just as they do in sarcoma. Hardly ever can a mammary cancer be examined without finding the veins of the tumor and its vicinity invaded by the disease. In the earliest stage the venous wall becomes adherent to the neoplasm; then it gets infiltrated, and its external coat is perforated. In the next stage the new growth projects more and more into the vein, being covered only by the intima of the latter. This soon yields, and the neoplasm—in the form of a small fungus—then projects into its lumen, when the growth may be detached *en masse* or in minute fragments. Cancer emboli of this kind have frequently been found free in the blood between the primary seat of disease and its derivatives and the right side of the heart, and even in the latter and in the pulmonary artery. Several trustworthy observers—Lücke among others—maintain that they have found cancer cells free in the blood. Nepveu claims to have discovered in the blood of cancer patients, numerous very minute corpuscles, which he maintains are the veritable elements of dissemination (*seminium cellulaire*). These bodies he derives from the cancer cells themselves, the nuclei and protoplasm of the latter both contributing to their formation. I shall have occasion to revert to this subject when treating of the cancerous cachexia. Meanwhile, I cannot refrain from remarking that the search for cancer elements in the blood—with the aid of modern high magnifying powers and improved technique—is a promising field of histological investigation that has as yet been but little worked.

That cancer emboli may develop into cancerous neoplasms, the well-known facts as to the autoinoculability of the disease conclusively prove (Hahn's experiments, and others).

We have now to inquire what it is that determines the development of metastatic tumors in certain localities rather than in others. There can be no doubt that the dissemination of cancer emboli is regulated by the same mechanical conditions that determine the distribution of ordinary emboli: from the veins at the root of the neck they pass to the right side of the heart, thence to the lungs; whence those small enough pass through the pulmonary capillaries, and so into the left side of the heart, and thence into the aortic system. It seems to follow from this—since the pulmonary capillaries are considerably smaller (0.007 to 0.008 mm.) than most cancer cells (0.010 to 0.050 mm. and upwards)—that the latter must almost invariably be arrested first of all in the lungs; and consequently that metastases must originate there, and that other organs can only be attacked through dissemination thence. But such conclusions are not in conformity with the results of actual observation, which show that the liver is more frequently the seat of metastases than the lungs; and that the latter often escape when other organs are invaded whose capillaries are larger than those of the lungs.* These and other phenomena of similar import indicate that the formation of metastases is conditioned by other considerations besides those of mere mechanical distribution.

The experiments of Maas and Cohnheim have shown that though fragments of postembryonic tissue, displaced from their normal surroundings and introduced into the bodies of other animals, grew at first, yet after a time they were invariably absorbed and completely disappeared. The reason for this evidently is that the foreign structures were ultimately unable to withstand the metabolism of the healthy tissues. In like manner I suspect most cancer emboli perish; but because some organs are less active in this respect than others, therefore they are more frequently affected with metastases. How otherwise can we explain the great frequency with which the liver is affected and the remarkable relative immunity of the spleen, both organs being equally exposed to the incidence of cancer emboli?† That cancer emboli frequently survive and develop into secondary tumors, in spite of the resistance of the tissues, evidently must be due either to their abnormal inherent activity or to falling off in the physiological capacity for resistance of the tissues. According to Cohnheim, it is wholly and solely due to the latter. In this I cannot concur.

The experiments of Féré, Zahn, and Leopold appear to me to point the other way. They have shown that transplanted grafts of *embryonic* tissues survive in spite of the physiological resistance, even to the extent of increasing two hundred or three hundred times in size. This is clearly due to the inherent activity of their constituent cells; and, as I have previously shown, it is with embryonic, rather than with postembryonic tissues, that actively growing cancer structures are comparable.

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* The passage of cancer emboli through the lungs, in spite of the above-mentioned difficulties, becomes intelligible when we consider the velocity of the flow, the distensibility of the capillaries, and the smallness of *young* cancer cells, which often measure considerably less than the figures given above (*e.g.* .003 to .004 mm.).

† The circulation through the portal system is very slow, especially through the liver. The liver, like the spleen, is comparatively seldom attacked by tubercle; but, unlike the spleen, it is a very suitable soil for the growth of malignant neoplasms.

From the foregoing it will be gathered that the ultimate fate of a cancer embolus—its complete absorption or its development into a secondary cancerous growth—depends mainly upon whether the inherent vital activity of its constituent cells is strong enough to resist successfully the phagocytic action of the part of the body in which it has lodged, or not.

Cachexia.

Consideration of the phenomena of cachexia naturally follows that of dissemination; because, as I shall proceed to show, just as the latter depend upon the entry of living cancer cells into the circulation, so the former likewise depend upon the entry into the circulation of the products resulting from their disintegration.

After a cancerous growth has existed for a variable time, which is generally rather long, the patient's health begins to suffer—even in the absence of ulceration, hemorrhage, etc. Pallor, weakness, emaciation, and loss of appetite are among the most obvious manifestations. These, as the disease progresses, become greatly aggravated—the pallor taking on a peculiar earthy or straw-colored tint—while other indications of profound disturbance of the general nutrition arise; which, when the malady runs its natural course, eventually determine death from asthenia.

The condition thus briefly sketched is that generally known as the cancerous cachexia. As a rule, it is more typically developed in connection with breast cancers than with those of most other parts of the body; yet in some varieties of the disease (*e.g.*, colloid and rodent ulcer) it is seldom seen. Sarcomatous tumors cause it less frequently than cancers. A similar condition is sometimes met with in connection with large intraabdominal tumors—especially with those of the uterus and ovaries. Hence there is nothing specific about it. The condition certainly cannot be attributed to the mere abstraction of nutritive materials from the blood, as some have suggested; for it is often met with in its most marked form in association with quite small cancerous tumors. Neither can it be ascribed to septicæmia; for it appears to be quite independent of such external lesions as usually accompany the ordinary septic infections *ab extrâ;* moreover, there is usually no pyrexia, but the temperature tends rather to be subnormal, and after death none of the usual signs of septicæmia are noticeable.

It is noteworthy that cachectic symptoms never precede the outbreak of the primary disease; from this we may infer that they are a consequence of its local progress. Certain it is that after removal of the disease by operation the cachectic symptoms often disappear, and in the absence of recurrence, patients may retain their healthy appearance for several years, as in cases I have observed. The degree of cachexia is, however, by no means always proportionate to the mere extent of the local malady, for I have seen well-marked cachectic symptoms supervene acutely, at an early stage, when the primary disease has been quite small. Neither can it be maintained that cachexia is dependent upon dissemination; for it may be absent when the latter is very marked, and *vice versâ*. Just so is it with regard to hemorrhage, which affects only a minority of cancer cases. In certain exceptional instances the disease may even run its entire course without ever causing any cachexia or other very obvious disturbance of the general nutrition, the patients being able to follow their usual avocations almost to the last. Indeed, cancer patients seldom take to bed until the disease has run more than half its course. The precise date at which cachectic symptoms are most prone to supervene and their sequence and degree of development are so variable that general statements respecting them cannot usefully be made.

We may, I think, best interpret these symptoms as the result of a general toxæmia, the explanation of which must be sought in the remarkable proneness of the constituent cells of cancers to undergo degenerative changes, which are often so extreme as to lead to their complete destruction by disintegration. When such excrementitious products find their way—by nutritive absorption or otherwise—into the general circulation, in quantities too great to be quickly eliminated and destroyed, they poison the fluids of the body; and so, by a kind of autointoxication, similar to that by which the system is infected from an inflammatory focus, they originate the phenomena of the cancerous cachexia. Hence these symptoms are much more frequently met with in association with cancers whose cells are specially prone to degenerative disintegration (*e.g.*, the breast) than with those whose cellular elements are more stable (*e.g.*, the lip). It seems probable that the excrementitious products thus produced contain toxic albuminoids analogous to the virulent substances secreted by microbes. Through these agencies the hæmatopoietic organs—especially the lymphatic apparatus—are injuriously affected. Thus the blood of cancer patients gets profoundly modified, both qualitatively and quantitatively. The red blood corpuscles show signs of progressive deterioration and destruction, while the white ones become much more numerous.

The most striking of these changes is the marked leucocytosis, the number of white corpuscles being increased, according to Hayem, from 6,000 per cubic millimetre—the normal standard—to 17,600 in certain cases of cancer of the stomach, to 11,400 in breast cancer, and to 7,800 in uterine cancer. Similar conditions have been demonstrated in connection with sarcomatous neoplasms. Hence it has been concluded that every tumor—unattended by inflammation or suppuration—that causes marked leucocytosis is due to malignant disease; but I doubt whether the proposition can be maintained in this absolute form.

In making use of this indication for diagnostic purposes, it is necessary to bear in mind that even in health the number of leucocytes presents considerable variations. Thus, after a meal, it is greatly increased; and there is a posthemorrhagic leucocytosis, as well as a leucocytosis of pregnancy, of the newly born, and of the dying. Moreover, similar conditions accompany inflammatory and febrile affections.

According to Schneyer and Hartung, the leucocytosis of digestion does not occur in cases of cancer of the stomach; whereas it is very noticeable in gastric ulcer, pyloric stenosis, and other non-cancerous morbid conditions. By this means it is claimed that the latter affections may be distinguished from cancer.

The initial diminution in the number of leucocytes (leucolysis), signalised by Löwit as invariably following the introduction of toxic substances into the circulation, has never been demonstrated in connection with the cancerous toxæmia; but it is nevertheless in all probability of constant occurrence, for the condition is a fleeting one.

The precise rôle played by each of the different varieties of leucocytes in the leucocytosis of cancer has not yet been satisfactorily determined. It is, however, generally ascribed mainly to augmentation in the number of lymphocytes, which are believed to be produced in excess by the irritated lymphatic organs. It has been determined by Zappert and others that the eosinophile corpuscles are decidedly diminished in numbers in this condition; but with regard to the part played by the polynuclear leucocytes (neutrophile of Ehrlich) and the mononuclear leucocytes (basophile of Ehrlich), nothing has yet been definitely ascertained.

It was long ago shown by Andral (1843) and Simon, that in cancer patients the red corpuscles of the blood are greatly diminished in numbers—even in the absence of ulceration and hemorrhage; and these results have been confirmed by recent investigators (Hayem and others). Thus, while the number of red corpuscles in a cubic millimetre of a healthy woman's blood is about 4,500,000, in cancer patients—even during the early stages of the disease—the number present is often less than 3,000,000, and at subsequent stages it may descend to 1,000,000 or even lower.

In healthy women the proportion of white to red blood corpuscles is about 1 to 750; but in those with cancer it varies from 1 to 380 to 1 to 60.

The poverty of the blood of cancer patients in hæmoglobin has been demonstrated by Quinquaud: 1,000 gms. of normal blood contain about 125 gms. of this substance, whereas in cancer cases the amount often does not exceed 25 gms. The difference between cancerous and non-cancerous blood in this respect is so marked and constant, that Laker maintains it may be relied on for the purpose of differential diagnosis. Marked diminution of hæmoglobin may be detected, even before any deterioration in the patient's general health is noticeable.

Various alterations in the form of the red corpuscles are also met with in the blood of the cancerous, most of which are due to degenerative changes (*e.g.*, microcytes and poikilocytes). Hayem maintains that the pseudoparasitic bodies, noticed in the blood by several observers, are mostly due to conditions of this kind (fragmentation, etc.). Probably the minute, highly refractile, amœboid bodies—found by Kahane in the freshly drawn blood, etc., of cancer patients—are also of this nature. Niessen claims to have discovered a mycete in the blood of cancer patients, intermediate between the mould and yeast fungi (canceromyces), which he regards as specific.

Blood plates ("Blutplättchen") are fairly numerous, except in advanced stages of the disease; but nucleated red globules (normoblasts) and megaloblasts are very rarely met with.

The quantity of albumin and inorganic salts dissolved in the serum is also less than the normal.

To the poverty of the blood in these and in other respects its diminished specific gravity may be ascribed.

On the other hand, its alkalinity is said to be increased; and an excess of saccharine matters is, according to Freund, of constant occurrence.

Such states of the blood explain the tendency, in advanced cachexia, to passive serous effusions (hydrothorax, anasarca, etc.), as well as to thromboses (of the pulmonary artery, iliac veins, etc.), phlebitis, and subacute inflammatory affections of the lungs.

They also enable us to understand how it is that great losses of blood are repaired so much more slowly in the cancerous than in the non-cancerous, to which Bierfreund has lately called attention.

Not only are the morphological and chemical constituents of the blood thus altered, but the experiments of Louis show that its total quantity is notably diminished. Thus may be explained the smallness of the heart, aorta, and arterial trunks, observed post mortem in most cancer cases that have run their natural course; although, as Beneke has shown, prior to the outbreak of the disease, cancer patients have large hearts and blood-vessels. Similar changes occur in the course of other chronic wasting diseases, especially in phthisis.

One of the most obvious manifestations of this depraved state of the blood is *pallor* of the skin; which, as the disease progresses, often assumes a waxy, puffy aspect, together with the peculiar straw-colored tint so characteristic of the cancerous cachexia. There is, however, nothing specific about it, for a similar condition is met with in other anæmic states, especially in chlorosis and in pernicious anæmia. It is probably due to altered hæmoglobin taken up by the plasma of the blood.

Inasmuch as the cancerous toxæmia sometimes gives rise to symptoms similar to those of pernicious anæmia, it may be mentioned here that in the latter disease there is no leucocytosis, but the red corpuscles are greatly diminished in numbers, even to a greater extent than in cancer; the hæmoglobin is also diminished, but in a less degree than might be expected, considering the great deglobulisation; moreover, nucleated red corpuscles and megaloblasts are common in pernicious anæmia.

A later developed manifestation is *emaciation*, which, when it has once set in, is steadily progressive, so that the wasting is often extreme. This, like most of the other individual symptoms of the cancerous cachexia, may, however, occasionally be absent.

Gastrointestinal disturbance is commonly experienced. Loss of appetite, dyspepsia, anorexia, together with thirst, are often prominent symptoms. Nausea and vomiting are also of frequent occurrence, even in the absence of visceral dissemination; and slight jaundice is not uncommon. Constipation oftener exists than diarrhœa. Aversion to nitrogenous food is frequently met with.

Pseudorheumatic pains in various parts of the body, remote from the primary seat of disease, such as the loins, hips, lower limbs, etc., are often complained of. When these coincide with subacute febrile disturbance, as occasionally happens, the condition may easily be mistaken for subacute rheumatism, of which I have seen several instances. Often pains of a neuralgic character are experienced, as well as numbness and tingling of the hands and feet; and an undue impressionability to cold may be noticeable.

Those who have examined cancer patients for *peripheral neuritis* have generally found it—*e.g.*, Gombault, Klippel, Arthaud, Auche, Isch-Wall, etc. Other observers (Cuffer, Riehl, etc.) have described various visceral vasomotor disturbances, which they attribute to inflammation of the sympathetic nerves. Herpes zoster is occasionally seen.

As the disease progresses cancer patients are apt to become irritable and depressed, but I have not noticed any special tendency to moroseness, on which Lebert insists. Headache and insomnia are of frequent occurrence, but the intelligence usually remains clear to the last.

In a few cases, after the disease has existed for a considerable time, cancer patients become *insane;* the form of mental derangement I have most frequently seen is that of dementia. Pinel mentions a case of this kind, in which the insanity was cured by removal of the cancerous disease.

Various symptoms also arise owing to disturbance of the sympathetic nervous system; among these I have frequently observed alternate flushing and pallor of the face and hands—sometimes so marked as to suggest Raynaud's disease—cardiac palpitation, syncope, shortness of breath, and gastric disturbance. I can also testify as to the correctness of Bogdan's observation that red patches are frequently visible on the cheeks, owing to dilatation of the superficial blood-vessels. These vasomotor disturbances are most marked in intra-abdominal cancers (*e.g.*, of the stomach and uterus).

Alterations in the blood, that involve considerable reduction in its hæmoglobin, as in phthisis, anæmia, etc., are usually associated—after a time—with widespread *fatty degeneration*, the result of impaired oxidation from diminished supply of oxygen. The cancerous cachexia is no exception to this rule. The parts most obviously thus affected I have found to be the liver, aortic arch, kidneys, large arteries, heart, etc.; but microscopical examination shows that similar changes are almost universal. The anorexia and constipation so frequently met with are largely due to changes of this kind affecting the liver and the gastrointestinal *mucosa.* I have found that the liver is more frequently thus affected, in an extreme degree, than any other organ; it happened thus in 17 out of my 44 breast-cancer necropsies, and in 21 out of my 78 uterine-cancer necropsies.

According to Rommelacre and others, the amount of urea, chlorides, and phosphates in the urine of cancer patients is decidedly below the normal, independently of alimentation. An excess of acetone has been noticed by Argenson and others. Gaudier and Hilt have lately shown that the urine of the cancerous is more toxic than normal urine, and in operated cases they have found that this toxicity disappeared after the removal of the local disease. Meyer comes to the same conclusion; and finds also that the splenic substance is highly toxic.

From the general malnutrition consequent on the cancerous toxæmia, the *bones* suffer as well as the other structures. Great interest attaches to these little studied changes, which require to be carefully discriminated from the lesions produced by cancerous dissemination, with which most pathologists have confounded them. According to my experience, the bones most frequently thus affected in a marked degree are the ribs, sternum, femur, cranial bones, humerus, and vertebræ. These, when affected, still retain their normal size and shape; but they are lighter and more fragile than they should be, so that they are easily fractured. Campbell's interesting experiments show that their breaking strain is very low indeed—often even four times less than the normal. There is thinning of the cortex, with increased size of the medullary canal, the cancelli and Haversian canals being much enlarged and filled with diffluent fatty matter; hence the undue porosity. The ends of the long bones are specially apt to be affected in this way. Altogether the indications point to defective deposition of new bone to replace the loss by absorption as the proximate cause of the condition.

Somewhat similar skeletal changes have been observed in many chronic wasting diseases, in the insane, in the aged, in pregnant women, and in chronic phosphorus poisoning.

Owing to this fragility of the bones, so-called spontaneous fractures are easily determined—in the absence of any cancerous dissemination; of this I have met with several instances.

It seems probable that the affection is in some way connected with alterations in the blood-forming properties of the red marrow; and it is a fact that the bones most frequently thus affected are just those in which hæmatopoietic functions are normally most active. In this form of mollities I have often noticed that the medulla has a gelatinous, diffluent, atrophic aspect, very different from its normal appearance; and it has been determined that its cells present no signs of proliferative activity.

A remarkable fact that may be mentioned here, is the rarity with which *amyloid degeneration* is associated with cancer; among my 44 breast-cancer necropsies there was not a single instance of it, and it was met with in only 4 cases out of my 78 uterine-cancer necropsies. In each of these instances the spleen was involved, and in 2 the liver as well.

It is now generally recognised that suppuration and ulceration are not essential precursors of amylosis, which may ensue from a variety of morbid conditions that seriously interfere with nutrition—*e.g.*, chronic intermittent fevers, malarial cachexia, large uterine and ovarian tumors, rachitis, gout, etc. Sarcomata also occasionally cause it.

In this connection great interest attaches to Krawkow's experiments on the artificial production of amylosis by the injection of cultures of staphylococcus pyogenes aureus; whence the author concludes that the amyloid material is a result of the constant poisoning and lowering of the organism by microbic products.

The comparative rarity and the slight intensity of the febrile complications of cancer is a noteworthy feature of the disease. When ulceration sets in and the wound is invaded by microbes, the ordinary symptoms of septic infection may be added to those of the cancerous cachexia. Considering the putridity that characterizes these ulcerating cancers, especially when the uterus is the part affected, septic complications are remarkably rare; but no doubt in certain cases they contribute their quota to the *ensemble* of symptoms. Hemorrhages and suppurations further impoverish the blood and weaken the patient.

At length, if the patient is not cut off by some intercurrent complication, death results from *asthenia.* It was thus that 64 out of 90 uterine cancer cases, that ran their natural course under my observation, terminated; and in 24 out of 40 fatal cases of breast cancer the end was similarly determined.

Recurrence.

No feature of cancer has attracted more attention than that which is known as "recurrence." It certainly does seem extraordinary, after everything has been done to insure its destruction—whether by the knife, by fire, or by caustics—that the disease should nevertheless so frequently spring up again.

Before attempting to explain this remarkable phenomenon, I propose briefly to set forth the chief known facts relating to it. In the great majority of these cases the recurrent disease makes its first appearance in the locality occupied by the primary disease, less frequently in the adjacent lymph glands, and—rarest of all—in remote parts of the body.

Thus, of 47 recurrent mammary cancers under my observation, the disease first reappeared in the primarily affected mammary region in 21 cases; in the mammary region and in the axillary glands, at about the same time, in 18 cases; and in the axilla alone in 8 cases.

According to Gross, of 496 local recurrences—294, or 59.27 per cent., were in the mammary region alone; 117, or 23.59 per cent., in the mammary region and the adjacent lymph glands; 77, or 15.50 per cent., in the adjacent lymph glands alone; 8, or 1.61 per cent., in the opposite breast.

Thus, of these 543 recurrent cases, the disease was situated in the mammary region in about 83 per cent., and in the axilla alone in about 15 per cent.

Local recurrences, when first noticed, usually present as small nodules, two or more in number; their initial situation being either in the operation scar or its immediate vicinity—rarely elsewhere. Recurrent lesions are much less frequently encountered in the cicatrix of the operation wound than in its vicinity.

Of Halsted's mammary-cancer extirpations, 6 per cent. recurred in the scar and 16 per cent. in the adjacent structures. By restricting the term "local recurrence" to recrudescence of the disease in the former situation, and by making a fantastic distinction between recurrence in the scar and in its vicinity—"regional recurrence"—Halsted has made it difficult to compare his results with those of other surgeons, who have not adopted his peculiar nomenclature.

Considering the frequency with which radical operations are now being done for uterine cancer, it is regrettable that the phenomena of its recurrence have not yet been studied with that thoroughness which is desirable. It has, however, been clearly ascertained that, in the immense majority of cases, the recurrent lesions make their first appearance in the locality of the primary disease, or in the region immediately adjacent thereto. Hofmeier finds that of 47 operated cases—in which recurrence took place during the first year after partial vaginal hysterectomy—in no less than 45 the initial manifestations were in the parametrium, and in only 2 in the uterine stump. Winter and other pathologists have fully corroborated these important observations. It appears to be rare for the initial manifestation of recurrence to originate in the ileopelvic or lumbar glands, but I know of no precise data bearing on this subject. Winter, however, specially states that after his numerous operations he never observed a single instance of the kind; and in 43 necropsies, after total extirpation of the cancerous uterus, he found glands involved in only 3. As to the relative frequency of recurrence in the ovaries, tubes, and adjacent parts of the broad ligaments, there is also lack of precise information.

Reappearance of the disease in parts of the body not directly connected with the primary neoplasm or its derivatives (so-called metastatic recurrence), was found by Gross to have taken place in 178 out of 1,036 mammary extirpations, or in 17 per cent.; but in 129 of these cases there was local or lymph-gland recurrence as well. With regard to uterine cancer, recurrences of this kind were met with by Winter only 7 times after 123 extirpations.

The *period* at which recurrences first present is exceedingly variable, and the numerical results obtained by different investigators are often divergent. Of 47 consecutive mammary cases under my observation, the average interval between the operation and the first obvious recurrence was 26 months, the maximum 130 months, the minimum a few weeks. These results are more favorable than those arrived at by my predecessors. According to Gross, the average period of immunity amounts to only 9.4 months.

These discrepancies are probably largely due to the variable stages of the disease at which operative interference was undertaken, and also to the diverse nature of the operative procedures themselves.

Thus Ott found, after 8 complete vaginal hysterectomies for uterine cancer during the early stage of the disease, that 7 patients were still free from recurrence for periods varying from 1 year to over 3 years, and in 1 patient the disease returned 1 year after extirpation; whereas, after 9 similar late operations, recurrence followed in every case in periods varying from 1 to 11 months.

Of 59 early operated cases, in which there were no signs of the disease having spread beyond the uterus, Leopold met with recurrence in 14, or in 23.7 per cent.; whereas of 68 advanced cases in which the parametrium, etc., was obviously involved, recurrence was found in 45, or in 66.1 per cent. Krakenberg's data are of similar import. These figures show the necessity for early operation.

The following tabular statement, based on 599 mammary cases, shows the periods at which recurrence may be expected:

Under 3 months	in 238 cases	(39.7 per cent.).
From 3 to 6 months	" 117 "	(19.5 ").
From 6 to 12 months	" 129 "	(21.5 ").
From 12 to 24 months	" 64 "	(10.8 ").
From 2 to 3 years	" 25 "	(4.2 ").
Over 3 years	" 26 "	(4.3 ").

The more elaborate analysis by Rieffel of 687 mammary cases yields very similar results, as the following table shows:

Interval between operation and first obvious recurrence.	Total number of cases.	Percentage numbers.
1st to end of 14th day	35	5.09
15th day to end of 1st month	91	13.24
2d month to end of 3d month	181	26.34
4th month to end of 6th month	137	19.94
7th month to end of 9th month	75	10.91
10th month to end of 12th month	52	7.28
13th month to end 18th month	54	7.83
19th month to end of 24th month	17	2.47
2d year to 2½ years	11	1.60
2½ years to 3 years	10	1.45
3 years to 4 years	15	2.18
Over 4 years	9	1.31
Total	687	99.64

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From these tables it will be gathered that over 60 per cent. of all mammary recurrences take place within the first six months after operation, and of these about 40 per cent. originate within the first three months. Over 18 per cent. occur within the first month, and 5 per cent. within the first fifteen days. The proportion of recurrences attributed by Gross and Winiwarter to the first month is considerably higher than the above-mentioned figure. Only about 4 per cent. of all recurrences originate after the third year, and after the fourth year the number is much smaller still. On the other hand, over 80 per cent. of recurrences originate during the first year after operation.

The following tabular statement, based on 144 cases of uterine cancer collected by Hache, shows the periods at which recurrence may be expected after complete vaginal hysterectomy.

Under 3 months.......	in 19.4 per cent.	12 to 18 months	in 12.5 per cent.
3 to 6 months........	" 18.0 "	18 to 24 months........	" 9.8 "
6 to 9 months........	" 10.5 "	2 to 3 years	" 14.6 "
9 to 12 months........	" 7.6 "	Over 3 years	" 7.6 "

From this we learn that over 55 per cent. of all recurrences belong to the first year, and that nearly 20 per cent. of these originate during the first three months. On the other hand, only 7.6 per cent. of recurrences appear after the third year.

Occasionally recurrence sets in *immediately* after operation, as in the following case:

A stout, healthy-looking woman, aged 68, with very large mammæ, came under my observation with a movable tumor of three months' growth, the size of a turnip, in the middle of her right breast. There was no obvious affection of the axillary lymph glands. The breast was amputated without opening the axilla. Immediately afterwards acute diffuse recurrence set in, which involved the whole wound. The skin, pectoral and intercostal muscles, ribs, and pleuræ, were quickly infiltrated. Six weeks after operation death ensued from hydrothorax and collapse of the right lung, owing to direct extension of the disease through the chest wall. At the necropsy the right parietal pleura was found to be studded throughout with cancerous nodules, and it showed signs of recent acute inflammation. The diaphragm and liver contained numerous secondary growths, but none were present in either of the lungs nor in the left pleura. It was a case of *acute traumatic malignancy* after operation.

At other times recurrence is delayed for many years—even for from twenty to thirty years; thus of 250 mammary cancer patients operated on by Velpeau, 20 remained free from recurrence for periods of from five to twenty-seven years, or 1 in 12½. Nunn and others have had similar results. Of the 47 recurrent mammary cases in my list, there were, however, only 2 instances in which the period of immunity extended to 10 years.

A striking example of the tardy recurrence of mammary cancer is afforded by the members of the family whose history Sibley has recorded, in which the mother and her five daughters all had cancer of the left breast. Two of these sisters passed eleven and twelve years respectively after removal of the primary disease without recurrence, and upon its return at those dates and repetition of the operation, each remained free from its return for seven years more, and they were still free when last heard of.

The longest period of immunity I know of is in a case reported by Verneuil, in which the disease recurred *in sitû* thirty years after amputation of the breast for the primary cancer. Bryant has seen similar recurrence after twenty-five years of immunity, and Nunn after sixteen years. Schmidt has reported an instance of death from cancer of the liver and lungs seven years after extirpation of the breast for cancer, with no local return of the disease.

The two following cases of late recurrence have come under my own observation.

CASE I.—An emaciated woman, aged 62, with a large hard mass of ulcerated recurrent cancer in the right mammary region, and cancerous glands in the axilla and lower part of the neck. About thirteen years ago she first noticed a lump in her right breast, which was amputated soon afterwards. Ten years subsequently several small recurrent nodules appeared in the vicinity of the scar and in the axilla. Two years ago these were excised. Six months later the present recurrence set in. No further operation was done. She died of pulmonary complications, apparently due to invasion of the chest by the local disease, some two and a half months later.

CASE II.—A well-nourished, healthy-looking woman, aged 58, with a nodule of recurrent cancer, the size of a hazelnut, at about the middle of the old scar in the left mammary region, and no obvious enlargement of the axillary glands. Twenty years ago she first noticed a small hard lump in the middle of her left breast. It slowly increased. Ten years later the breast was amputated. She remained quite free from any return of the disease until six months ago, when the present recurrence was first noticed. It was excised, and the wound had healed a fortnight later.

Such cases illustrate the extraordinary differences that obtain, in relative malignancy, between cancers of the same variety—morphologically indistinguishable—in the same locality and apparently under similar conditions.

In uterine cancer it is very exceptional for the disease to reappear, after total hysterectomy, at a later period than four years after the operation. Cases of late local recurrence are, however, much commoner after partial operations.

Recent experience has shown that the relative frequency of recurrence and the date of its supervention are determined mainly by the nature of the operation done for the removal of the primary disease. It was formerly customary at such operations to remove only the local tumor as a palliative measure, the disease itself being regarded as incurable. Thus, writing about 1750, Alexander Monro says that of sixty cancer patients treated in this way, only four remained free from recurrence for upwards of two years afterwards. Winiwarter, analysing the results of Billroth's numerous breast-cancer operations up to 1876, found that only 5.6 per cent. of patients who had survived the procedure were free from return of the disease for upwards of three years afterwards, there being 85 per cent. of local recurrences; these results he regarded as surprisingly good, for no such favorable data had up to that time been published. The much more favorable results of modern operators are the natural outcome of the greatly improved knowledge of the pathology of the disease that now prevails, for which we are largely indebted to Virchow. He taught that cancer in its beginning, and often for long afterwards, is a local disease, and that consequently it must be possible during this period to cure it locally. In accordance with this doctrine Charles Moore, as early as 1867, advocated and practised far more thorough and extensive operations than had hitherto been customary, with the object of completely extirpating and so of curing the disease. However, in spite of this, British surgeons—then, as now, the slaves of routine—continued, as heretofore, to be satisfied with partial operations, in which the adjacent glands were seldom removed. The excellent results obtained in Germany by Moore's method (Volkmann and others) at length compelled reconsideration of the subject. Its reintroduction into this country dates from the publication of Banks' experience in 1882, while in the United States the practice of Gross tended to the same end. Earlier and more thorough operations than were formerly customary are now the order of the day.

The effect of these improved methods of operating on the incidence of recurrence has been very striking: thus the liability to local recurrence, after the extirpation of mammary cancer, has thereby been reduced from over 80 per cent. to from 50 to 20 per cent. (Bergmann, Banks, Czerny, Krönlein, Halsted, etc.), while at the same time the proportion of patients well and free from any return of the disease, for upwards of three years afterwards, has increased from 5 per cent. to from 20 to 30 per cent. (König, Küster, Banks, Gross, Dennis, Bull, Halsted, Bergmann, etc.).

Another effect of thorough operations has been to add considerably to the duration of the life of those who have survived them.

I have tabulated all the fatal cases of breast cancer that came under my observation at the Middlesex Hospital during a period of six years, with the result that the average duration of life—dating from the time when the disease was *first noticed*—was 60.8 months for those who underwent operation, and 44.8 months for those in whom the disease ran its natural course. Thus the average duration of life for the *operated* cases was 16 months longer than for the non-operated, and after extirpation of the primary disease the former lived—on the average—for 40.3 months; that is to say, nearly as long as the entire duration of the life of the non-operated. Moreover, the number of those who died before the end of the third year after operation was 40 per cent., whereas of the non-operated the number who died prior to this period was 53 per cent.

In cancer of other localities, equally good results have followed bold attempts to completely extirpate the disease; so that no one nowadays doubts the propriety of such proceedings, which surgeons are constantly striving to improve, and withal successfully. We are thus justified in taking a much more favorable view of the prognosis of cancer than our forefathers did. Had Hippocrates been aware of modern achievements in this direction, he would certainly have written his celebrated aphorism, relating to the operative treatment of cancer, very differently.

Second recurrences are fairly common. I have met with them in 8 out of 43 recurrent mammary cases (18.6 per cent.), and Rieffel in 134 out of 687 such cases (19.5 per cent.). The earliest date at which second recurrences appeared, in the 8 cases under my observation, was a few days after the operation; the latest, 130 months after; and the average interval was 23.2 months. In these same 8 cases the first recurrence appeared, on the average, 41.5 months after operation. This supports Thiersch's dictum that the interval between operation and recurrence tends to shorten with each successive operation.

Third recurrences are rare: there was only 1 instance of the kind among the 43 recurrent mammary cancers of my list (2.3 per cent.), and 30 among Rieffel's 687 cases (4.3 per cent.).

Fourth recurrences are so highly exceptional that Rieffel's list of recurrent cases comprises only 7 instances, or rather more than 1 per cent.

Many instances of the cure of cancer, even after two or more operations, have been reported: Plicque has lately collected the records of 97 cases of this kind. Poulsen has also reported instances in which, during the first year or two after the first operation, one or more recurrent tumors have been removed, yet the patients were well and free from any return of the disease from eight to nine years after the last operation; and Gouley has met with 2 cases of recurrent breast cancer, under observation twenty and twenty-five years respectively after the first operation, in which the patients were well and free from recurrence when last seen—upwards of five years after the last operation.

Careful examination of recurrent growths has revealed the important fact that in their morphological and other characters they closely resemble the primary neoplasm. From this we may infer that they originate from the latter or its derivatives, or that both alike spring from the same source. These are, in fact, the sole sources of recurrent growths.

Very significant is it that the great majority of recurrences are situated either in or in the immediate vicinity of the operation wound. In the case of mammary cancer the researches of Volkmann, Heidenhain, and others have conclusively demonstrated that fragments of the original disease are almost invariably left behind after operations undertaken for its removal, as hitherto usually practised.

After the removal of uterine cancer, even by total hysterectomy, Leopold, Mackenrodt, and others have shown that unextirpated fragments of the disease are frequently left behind. It seems certain that morbid fragments of this kind, persisting after operation, are the germs whence most recurrent growths originate. Thus may be explained the *initial multiplicity* of most recurrences, wherein they differ so markedly from independent spontaneous outgrowths, which are almost invariably solitary.

The great frequency of recurrences soon after operations points in the same direction. Hence we may conclude that the immense majority of local recurrences are due to incomplete ablation of the primary growth. In these cases there is indeed no real reproduction of the disease, but merely continuation of it in the surviving unextirpated fragments (*continuation recurrence*). Similarly, when after operation the disease recurs in adjacent lymph glands or in remote parts of the body—apparently unaffected before—we may infer that its recrudescence in these situations is generally due to the dissemination there of fragments of the primary disease prior to the operation for its removal, these having subsequently developed, as in the formation of other disseminative growths.

It seems not improbable that some of these local recurrences are due to inoculation of the operation wound with cancer elements, detached by the surgeon's knife, etc. To avoid this, Donitz, Sabatier, and others recommend that care should be taken not to cut into such neoplasms during their removal.

Hofmeier, Winter, Schopf, and others believe that many of the recurrences after vaginal hysterectomy for uterine cancer are thus caused. Winter is especially inclined to ascribe to this source those cases of diffuse recurrence in the parametrium that are not infrequently observed after hysterectomy. While not wishing to overlook this danger, it seems to me more in accordance with the present state of knowledge to ascribe the origin of most continuation recurrences to the survival of unextirpated fragments of the primary disease in the surrounding parts, rather than to traumatic dissemination.

There yet remain for consideration those instances of *late* recurrence occurring several years after operation—of which I have previously described several instances—which cannot be explained in this way without resorting to the gratuitous assumption that cancer elements may lie dormant in the tissues for several years, and then suddenly recover their morbid activity. Such cases—which are rare—are, I think, undoubtedly due to independent outbreaks of the disease (*repullulation*) in unextirpated remains of the glandular structures of the part in which the disease originated; these—as many observers have now demonstrated—are always in a hyperplastic condition (precancerous). This explains the almost invariable localization of late recurrences in the primarily affected region, rather than elsewhere; and their more frequent appearance in the vicinity of the operation wound, rather than in the scar itself.

Certain highly exceptional instances of late recurrence, which cannot be satisfactorily explained by any of the foregoing rationales—such as Schmidt's case of the occurrence of cancer in the liver seven years after extirpation of the primary disease from the breast—are probably due to the lodgment of hyperplastic, precancerous cells—derived from the mamma at the time of the operation—in the liver, where they have subsequently taken on cancerous activity. The experiments of Schweninger, Kaufmann, and Ribbert have demonstrated the vitality of such grafts and the facility with which they persist and develop. In like manner cancer is sometimes seen to arise primarily in the glands of the groin, in association with precancerous lesions of the penis and scrotum. The development of cancer from cells detached and implanted in the cicatrix of the wounds made for the removal of non-malignant ovarian cysts, long after the successful completion of the operation, is a phenomenon of similar import (Pfannenstiel's cases, etc.). I would suggest an explanation of this kind for those rare instances of late recurrence after total hysterectomy for uterine cancer, when it is hardly conceivable that any unextirpated remains of the utricular glands could possibly have been left behind. In these cases, however, the recurrent disease may very well have arisen from non-cancerous epithelial cells, detached during the operation and grafted in the vicinity. I certainly think this explanation is more in accordance with the known facts than the alternative one of latent cancer germs, which has no definitely ascertained facts to rest on. There is still another source whence certain late recurrent growths occasionally arise, and that is from aberrant epithelial sequestrations ("rests"), which are often of embryonic origin.

I have elsewhere ("Diseases of the Breast," London, 1894) directed attention to the almost invariable occurrence of extensions of the mammary gland into the axilla, which are often completely sequestrated, and to the frequency with which cancerous and other neoplasms originate from these sequestrations.

I have met with several instances of the late recurrence of mammary cancer in the axilla, evidently due to the independent outbreak of the disease in such outlying extensions or sequestrations. In like manner primary axillary cancers arise. The following cases will suffice to illustrate this condition:

Case I.—A woman, aged 59, first noticed a cancerous tumor in her left breast nine years ago. Seven years ago the part was amputated, but the axilla was not touched. She remained quite free from any return of the disease until two months ago, when a hard cancerous lump formed at the upper and inner part of the left axilla; the scar in the mammary region and its vicinity was entirely free.

Case II.—In a patient, aged 48, four years after the amputation of her right breast for hard cancer, the disease reappeared in the right axilla, the scar in the mammary region and its vicinity being quite healthy. At the time of the primary operation the axilla was not touched.

It is probable that certain cases of late recurrence in the mammary region, arising at some distance from the operation scar, also originate from aberrant glandular sequestrations. Similarly, certain late recurrences after total hysterectomy for uterine cancer may also arise, in an analogous manner, from aberrant remains of Wolffian or Müllerian structures, embedded in the periuterine tissues.

Varieties of Cancer.

As I have previously mentioned, the kinds of cancerous disease likely to arise from any particular part of the body are mainly determined by the local peculiarities.

VARIETIES OF MAMMARY CANCER.

In the *breast*, for instance, I discriminate two species: (1) the *acinous*, which arises from the secretory parts of the gland; and (2) the *tubular*, which arises from its ducts.

Acinous cancers may be of the acute, chronic, or melanotic variety.

The Acute Type.

Although cancer of the breast is usually a chronic disease, yet certain cases occasionally run an acute course. Of these the following types may be recognized:

A very rare diffuse form—denominated *cancer d'emblée, squirrhe ligueux en masse* by Velpeau, and *mastitis carcinomatosa* by Klotz—in which the whole of one or both breasts may be at once involved. It arises suddenly, progresses rapidly, and is often accompanied by inflammatory phenomena. No special tumor is formed, but the whole breast becomes enlarged and hard, the skin reddened, œdematous, and adherent, and the subcutaneous veins are unduly visible. Verneuil and Estlander found the temperature of the affected skin from one-half to two degrees above the normal; and the former has demonstrated, in some cases, a veritable cancerous fever. The adjacent lymph glands are usually soon invaded, and there is general dissemination of the disease, with death from acute cachexia. Its total duration seldom exceeds a few months, and instances have been reported by Billroth and Aitken in which it proved fatal within six weeks. Most cases—but not all—arise in connection with pregnancy or lactation; under these circumstances the disease is apt to be mistaken at first for acute mastitis.

Examples of this type of acute cancer have been reported by Terrillon, Kantorowicz, Monod, Volkmann, Klotz, and others.

Although I do not regard the *squirrhe tégumentaire* of Velpeau as a distinct variety, but merely as a peculiar form of cutaneous dissemination of ordinary acinous cancer, yet it will be convenient to describe it here. Acinous cancers that originate beneath the nipple and areola are specially prone to be followed by acute dissemination in the skin, owing to early implication of the subareolar lymphatic plexus, and rapid diffusion of cancer cells through its communicating cutaneous branches. Lesions thus induced assume the form either of small tubercles (*squirrhe disseminé, acute miliary carcinosis*), of irregularly shaped discs (*en plaques*), or of diffuse infiltrations (*en cuirasse*). Velpeau, who first clearly differentiated these conditions, thought that some cases were from first to last limited entirely to the skin; but most pathologists are now agreed that the cutaneous infiltration is invariably secondary to primary disease of the breast. Cases of this type run a rapid course, and are exceedingly malignant. According to Estlander, the average duration of life seldom exceeds from five to twelve months. This estimate is no doubt true for those cases in which the skin is implicated at an early stage of the disease; but I have seen instances in which cutaneous dissemination did not supervene until several years after the onset of the primary disease in the breast.

Of one hundred and seventy cases of mammary cancer consecutively under my observation, there were only two instances of *squirrhe disseminé.* The following is a typical example:

A pale, weak, emaciated woman, aged 32, the mother of five children, had a small, hard tumor in the left breast, of one month's duration. The overlying skin was adherent, and it contained an immense number of small cancerous nodules, varying in size from a pea to a pin's head, which were in some places confluent. The skin of the parts adjacent to the left breast was similarly affected, as well as that of the left axilla, where the lymph glands were enlarged. In the course of the next few months the opposite breast and the whole of the integument of the front of the chest were similarly invaded. No operation was done. She died thus of asthenia, with symptoms of intrathoracic dissemination, seven and a half months after the disease was first noticed. She was of a very tuberculous family, both her parents and three of her brothers and sisters having died of phthisis; but there was no family history of cancer.

In the *diffuse* form the onset is generally insidious and painless, like that of ordinary cancer. Too often nothing wrong is noticed until the disease has made considerable progress. The first thing to attract attention often is the presence in the mammary skin of one or more dusky-red, erysipelatous-looking, hard *plaques.* These may be accompanied by a feeling of heat and burning, together with a vague sense of discomfort, sleeplessness, and loss of appetite. As the disease progresses, these indurated areas increase and coalesce, thus converting the skin into a hard, coriaceous structure of dusky red color, and fixing it firmly to the subjacent parts. This leather-like transformation often extends far beyond the region of the originally affected breast. It may even involve the skin of the whole trunk, transforming it into a constrictive *cuirasse*, as in one of Velpeau's cases, which he describes as follows:

"Toute la poitrine, depuis les flancs jusqu'au cou, depuis l'ombilic jusqu'au larynx, depuis les lombes jusqu'à l'occiput, avait subi la transformation ligneuse et était en outre criblée d'ulcères squirrheux, avec une foule de bosselures cancéreuses, jusque dans les aisselles et sur les épaules. Cette pauvre femme, dont les deux bras était triplés de volume et durs comme du marbre, avait la respiration si petite, si courte, qu'elle ressemblait à une personne qu'on étrangle, ou dont la poitrine est violemment prise dans un étau; ne pouvant remuer ni les bras, ni la tête, éprouvant des douleurs atroces à tout instant, elle offrait, quand je la vis, le spectacle le plus navrant qui se puisse imaginer," etc.

Soon death ensues, which is generally due either to acute cachexia, to extension of the disease to the thorax—causing hydrothorax, etc. —or to constrictive dyspnœa, owing to mechanical interference with the respiratory movements. Histological examination of the thickened skin shows that the corium is infiltrated with cancerous new formation, consisting of irregular aggregations of polyhedric or variously shaped epithelial cells, closely packed, without definite arrangement, in the irregularly shaped meshes of a fibrous reticulum. These meshes appear to be dilated lymph spaces. There is seldom any definite alveolar formation, and sometimes the spaces contain only a single file of cells. The epidermis is unaffected. I have described in the *Medical Press and Circular* for October 29th, 1884 ("Two Cases of Acute Diffuse Strangulating Cancer of the Neck"), two examples of similar disease in the neck, which probably originated in connection with epithelial remains of the branchial clefts ("branchiogenic cancer").

Of 170 cases of mammary cancer consecutively under my observation, there were only 3 instances of this cuirassed form of the disease. According to Gross, it is met with once in every 22 cases.

I would here call attention to certain cases of mammary cancer, which, although they in no way differ morphologically from ordinary acinous cancers, nevertheless run a very acute course. I have met with 6 such cases out of 64 consecutively fatal breast cancers. The following is a typical example:

A moderately nourished, single woman, aged 30, five months ago first noticed a hard lump, the size of a bantam's egg, in the axillary segment of her right breast. On examination, I found in this situation a hard mass of new growth, the size of half an orange, adherent to the chest wall and to the overlying skin. The glands of the right axilla were extensively infiltrated and matted together. The family history was good. No operation was perfomed. She died of asthenia about five and a half months later. At the necropsy the body was seen to be greatly emaciated. A large ulcerated cancerous growth occupied the right breast, and the adjacent soft parts were infiltrated. The growth was of firm, whitish scirrhous structure. The sternum and adjacent pleura were infiltrated with a similar growth. The liver contained numerous secondary nodules.

The Chronic Type.

Mammary cancers that take more than five years to run their entire course, I reckon as of the chronic variety. Such cases are much commoner than is generally supposed, and what is still less appreciated is that the great majority of them are morphologically indistinguishable from ordinary acinous cancer (scirrhous).

Of 170 women with mammary cancer consecutively under my observation, in no less than 31 (18.2 per cent.) the disease was of the chronic type; and in 25 the growth was morphologically of the ordinary acinous kind.

The disease in these 25 *chronic acinous cancers* had already lasted as follows: 5 to 10 years in 14 cases; 10 to 15 years in 6 cases; 15 to 20 years in 2 cases; 20 to 25 years in 1 case; over 25 years in 1 case.

Similarly of 64 consecutive *fatal* cases that had run their natural course, in 17, or 26.5 per cent., the disease had lasted upwards of five years; and of these 14 were of the ordinary scirrhous type.

The total duration of life in these 14 chronic scirrhous cases was as follows: 5 to 10 years in 8 cases; 10 to 15 years in 5 cases; over 20 years in 1 case.

I have had cases in which the disease had lasted for twenty-eight, twenty-four, and seventeen years respectively. Nunn has lately reported an instance of chronic breast cancer, in which the total duration of the disease had exceeded thirty years; when last seen the patient was still able to earn her living as a charwoman.

In point of chronicity it would be difficult to surpass such cases, even among the atrophic and colloid varieties of the disease, which are generally supposed to have a monopoly in this respect.

The *atrophic* form of cancer is certainly rare, for of 170 consecutive mammary cancers I met with only 6 instances of it, or 3.5 per cent. According to Gross, atrophic varieties constitute about 7.9 per cent. of all breast cancers.

The characteristic feature of this type is the continuous, gradual shrinking of the new formation, and the consequent irregular contraction of the breast, which is often thereby diminished rather than increased in size. The deformity produced is apt to resemble that met with in "chronic cirrhosing mastitis." The atrophic, cicatrizing, or cirrhosing cancers usually begin with obscure hardness, which progresses slowly, forming at length ill-defined, flattened, or irregularly nodulated thickening, with numerous "roots" stretching far into the adjacent parts. Such growths consist of very dense, whitish, dry, fibroid substance; and on account of their extreme hardness they have not inappropriately been designated "stone cancers."

Histologically the fibrous stroma preponderates, while epithelial elements are very scanty or altogether wanting. This stroma consists of irregularly disposed bundles of fibrous tissue, rich in elastic fibres, but poor in cellular elements. It contains variously shaped small spaces—atrophied alveoli—in which are a few degenerate epithelial cells, or merely cellular *débris* and fatty granules. The constituent cells of cancers of this kind are very short-lived, for no sooner have they formed than they thus degenerate; only at their extreme periphery are proliferous epithelial cells to be found.

A notable feature of atrophic cancer is the marked deformity of the breast, caused by the shrinkage of the neoplasm; at first only the nipple and skin are retracted, but finally the latter is thrown into obvious plications. The subcutaneous veins are seldom seen distended, as in ordinary cancers. Usually the disease runs an extremely chronic course, most cases lasting for from ten to fifteen years or more; but spontaneous cures are, nevertheless, unknown. Here I may mention that I have met with several typical examples of atrophic cancer, which have seemed to run their entire course in less than a year.

The general health of women with atrophic cancer usually remains unimpaired for a long time, but at length cachectic symptoms supervene. Shallow indolent ulcerations often result, which occasionally partially cicatrize. Old women are said to be particularly liable to atrophic cancer, but this is only partially true. Most cases supervene at a more advanced period of life than ordinary scirrhus; but, as Gross has pointed out, quite fifty-five per cent. originate before the age of fifty.

Atrophic cancers are specially prone to invade extensively the adjacent tissues by direct extension and in a less degree by local dissemination. Lymph-glandular and general dissemination, although often long delayed, are seldom absent; and recurrence after operation is of frequent occurrence. The secondary growths reproduce the atrophic characteristics of the primary one.

There can be no doubt that under the term *colloid cancer* several different varieties of malignant disease having a gelatiniform aspect, are commonly included. The subject requires to be thoroughly reinvestigated, in the light of modern science. Most of the seventy-five mammary cases collected by Lange are of ancient date, imperfectly recorded, defective in histological details and in other respects.

The disease is certainly rare, since of 170 consecutive mammary cancers I have not met with a single instance of it. Lange estimates that only 0.93 per cent. of all breast cancers are of this variety; and Gross' estimate is 1.34 per cent.

The disease owes its peculiar features to the proneness of its constituent cells to undergo colloid metamorphosis. In this connection it must be remembered that colloid changes normally occur in the secretory cells of the gland during the early stages of lactation.

Colloid cancer of the breast is remarkable for the slowness of its progress.

Sections of such growths reveal small, translucent collections of glutinous fluid, embedded in the meshes of a fibrous stroma, in place of the usual opaque cellular aggregations. It comparatively seldom happens, however, that the whole neoplasm is thus affected; for some parts nearly always retain their ordinary scirrhous character.

The process begins with the formation, within the cells, of clear colloid globules. As these increase the cells perish; the freed globules then coalesce, and so form the larger colloid masses. Other of the cells undergo hyaline, fatty, and calcareous changes (Olivier, Neugebauer, etc.). Thus all the cancer cells of a wide area may perish, the stroma being the only formed constituent left. In other parts of the same growth regions may be found in which the cells are merely fringed with colloid changes; and in yet other localities no colloid change may be noticeable. As the disease progresses the fibrous stroma often becomes œdematous, and much of it may eventually disappear, leading sometimes to cyst formation. Histological sections show large, thin-walled alveoli, distended with colloid fluid containing granular *débris*, in which only a few degenerated cells, or perhaps none at all, can be made out. Owing to these changes in the cells their growth is retarded, and the malignancy of the disease is thereby diminished; hence colloid cancers run a very chronic course, the average duration of life being about twelve years; and they are more tardily and less frequently followed by local, lymph-glandular, and general dissemination than any other form of mammary cancer. Moreover, in this variety of the disease cachectic symptoms seldom supervene. When secondary growths do arise, in their main features they resemble the primary ones.

Colloid cancer usually begins as a small, lumpy swelling in the breast, which increases very slowly. The resulting tumor seldom exceeds the size of a hen's egg, and it may take from ten to fifteen years to attain this size. It generally feels firm and elastic, with projecting bosses. As these growths do not shrink, the nipple and overlying skin are much less frequently retracted than in ordinary scirrhus. Ulceration occasionally ensues at an advanced stage of the disease. Recurrences are less frequent than after the removal of any other form of mammary cancer; and when they do occur they are of tardy development, rarely supervening until from three to ten years after operation.

The average age at the onset of the disease is forty-seven years, and in about half the cases it begins after fifty.

Many cases of so-called colloid cancer of the breast are really examples of *carcinoma myxomatodes*. In this variety of mammary cancer the gelatinous transformation is due to myxomatous metaplasia of the fibrous tissue of the stroma, and in extreme cases of its cellular elements as well. Exceptionally it may even happen that the cancer cells themselves thus degenerate. In this connection it should be borne in mind, that a layer of mucoid connective tissue is normally present immediately around the ducts and acini. Eve has specially studied this variety of the disease, of which Edmunds also has described an instance.

A subvariety arises—to which the term *cylindroma* has been applied —in which the mucoid stroma grows into the epithelial masses and becomes more or less enclosed in them; of this variety a few instances have been recorded.

The Melanotic Type.

Any form of melanotic neoplasm of the breast is of extreme rarity. My table of 2,397 consecutive primary neoplasms of the female breast does not contain a single instance, and Gurlt's 1,608 mammary cases includes only a single example—a melanotic cancer. It appears, however, to be rather less exceptional in the male breast, for of 100 primary cancers of this part tabulated by me, 3 were of the melanotic variety. Examples of acinous melanotic cancer of the female breast have been reported by Billroth, Cornil, and Ranvier. Several instances of melanotic cancer, arising from the mammary integumental system, have also been published (Curtis, Wacker, etc.). The Hunterian Museum contains a specimen (No. 469 of the Pathological Series) of melanoma of a white cow's udder.

Tubular Cancer.

As I have elsewhere pointed out, under the term "villous duct cancer," as hitherto commonly employed, at least two perfectly distinct kinds of mammary neoplasm are included—viz., the *non-malignant villous papilloma* and the *tubular cancer*. The latter term is applied by me to certain cancers, originating from the mammary ducts, which histologically consist of duct-like tubular structures. Cysts and intracystic growths, seldom found in association with acinous (scirrhous) cancer, frequently arise in connection with the tubular form. Histologically the latter is characterized by the presence of elongated, intercommunicating, cellular processes, growing into the surrounding connective tissue. These processes have the form either of hollow tubes, lined with one or several layers of columnar epithelium, or of solid cellular cylinders, of which at least the peripheral cells are of the columnar type. In cross sections duct-like structures are seen; or solid, rounded, quasi-alveolar, cellular aggregations. In connection with these, numerous small cysts frequently arise, through granulofatty disintegration of their cells; and within the cysts papillary growths often spring up. From the columnar type of their cells, and from the tubular form assumed by the ingrowths, it may be inferred that these neoplasms originate from the mammary ducts. Growths of this kind generally present as hard, nodulated, irregular tumors, which are usually circumscribed, and often more or less completely encapsuled. They vary in size from a hazelnut to a new-born child's head; and commonly they are as large as a hen's egg. They are generally mobile, and very seldom do they cause retraction of the nipple or of the overlying skin. On section we find them composed of firm, whitish—or, in places, pale pinkish—solid substance, formed by the ingrowing epithelial processes; with here and there yellowish areas, out of which a pultaceous substance—consisting of epithelial cells in granulofatty degeneration—may be squeezed. There is complete absence of fatty tissue, and the stroma is scanty. Embedded in this solid substance are numerous minute cysts. Sometimes the latter are so numerous as to convert the tumor into soft reticular substance. These cysts, some of which occasionally attain rather large size, contain mucoid or pultaceous fluid and not infrequently intracystic papillary growths. In this connection ecchymoses and hemorrhages may arise.

Their clinical history is a matter of great interest. The chief points are these: They occasionally disseminate in the adjacent structures. In a case recorded by Shattock, nodules of this kind were found adherent to the two upper ribs in a woman, aged sixty, who died a few weeks after amputation of the breast for the primary disease. They have been found frequently to recur locally after removal. This is known to have happened in eight out of my eighteen cases.

The adjacent axillary lymph glands are occasionally infected by these neoplasms. This occurred in five out of my eighteen cases.

To account for the comparative rarity of lymph-gland dissemination, Labbé and Coÿne have pointed out, that between the proliferating epithelial zone and the nearest lymphatic lacunæ, a barrier of thick fibrous tissue exists, which must be overcome before the cancer cells can gain entrance into the lymphatics. The slowness with which this is effected indicates, I take it, the low degree of malignancy of the new growth, rather than the strength of the intervening barrier. These neoplasms sometimes cause general systemic dissemination; my list comprises two cases of this kind.

Tubular cancer supervenes at a much later period of life than villous papilloma, and even than acinous (alveolar) cancer. The average age of my cases, at the onset of the disease, was 53.5 years; the oldest, 65.5; the youngest, 40. The numbers for each quinquennial period were as follows: 40 to 45 years in 4 cases; 45 to 50 years in 3 cases; 50 to 55 years in 2 cases; 55 to 60 years in 4 cases; 60 to 65 years in 5 cases; 65 to 70 years in 1 case.

The first symptom of the disease usually is the presence of a small tumor in the central part of the breast, beneath the nipple or areola. The serosanious discharges from the nipple, so characteristic of villous papilloma, are seldom met with.

Tubular cancers increase much more rapidly than villous papillomas; in less than a year they commonly attain the size of a hen's egg. Occasionally they burst through the overlying skin, and fungate. In my list there are four cases of this form of cancer, in which tumors had been present for long periods, viz., thirty-six, eighteen, fifteen, and seven years respectively. In each of these cases a small tumor had existed for most of this time—whose increase was almost imperceptible—and then during the last few years it had rapidly attained large size. There are several facts about the history of these cases that make me think we have here to do with tubular cancer supervening on villous papilloma of many years' standing, of which I have met with a typical instance.

The Varieties of Uterine Cancer.

In the *uterus* three varieties of cancer may be recognized: (1) the *glandular*, which arises from the cylindrical epithelium of the glands of the cervix or of the corpus; (2) the *epidermoidal*, which arises from the rete of the epidermis of the portio; and (3) the *endothelial*, which arises from the intima of the lymphatics or blood-vessels, or from the perithelium.

Glandular Cancer.

Glandular cancers that run their entire course within a year, I reckon as of the *acute* variety. Such cases are by no means rare; of my 90 uterine cancers, 24 were acute, or 26.6 per cent., whereas only 15.6 per cent. of my mammary cancers proved fatal within this brief period. The morphological characteristics of such growths are usually identical with those of the ordinary cylinder-celled glandular cancer. In some exceptional cases, however, the morbid epithelial elements, instead of assuming the typical tubular form, have been observed to be irregularly diffused in the surrounding stroma, as in certain acute cases of mammary cancer. I have seen it stated that uterine cancers of this kind are commonest in young women recently pregnant. My experience gives no support to this statement. In not a single one of my acute cases did the disease start prior to the age of 30; 6 patients were over 40, 2 over 50, and 1 was 68½ years old at the onset of the disease. In none of my cases did the beginning of the disease coincide with or occur soon after parturition. These facts indicate that the abnormally rapid progress of the neoplasm depends more upon the intrinsic properties of its constituent cells than upon extraneous influences. The most rapidly progressive case of my list ran its entire course in 4.7 months. Kiwisch has reported an instance in which the total duration was only 5 weeks, and Lebert's acutest case died within 3 months from the date of outbreak. As in the corresponding variety of mammary cancer, widespread dissemination often occurs.

Chronic cases—that is to say, cases in which the total duration of the disease exceeds three years—are rarer than acute ones. Of my 90 uterine cases, 15, or 16.6 per cent., were of this kind. In 3 the total duration of life exceeded 7 years. My most chronic case lasted over 7½ years, when the patient, aged 52, died suddenly from the bursting of a pyonephrosis into the peritoneal cavity. The structural characteristics of these chronic growths differed in no respect from those of the ordinary cylinder-celled glandular cancers. The average age of the patients was 51 years; that for uterine cancer in general is only 44 years. F. Barker has reported an instance of uterine cancer in which the disease lasted for 11 years.

Colloid cancer of the uterus is an exceedingly rare affection. I have elsewhere given an account of the only case of the kind I have ever met with. In his monograph on neoplasms of the cervical part of the uterus Amann describes only a single uterine case. Menge has since reported another example. Wagner and Lebert have both met with the disease. In my case it seems probable that the disease arose from "rests" of the rectal mucosa, embedded in an adjacent myoma of the uterus; other cases probably arise from ovarian "rests." I doubt whether primary colloid cancer of the uterus ever occurs otherwise than in connection with aberrant elements of this kind.

Primary *melanotic* neplasms of the uterus are of extreme rarity. Whitridge Williams, writing in 1894, could cite only four instances, most cases arising from the portio.

Epidermoidal Cancer.

Certain epidermoidal-celled cancers of the portio occasionally give rise to very chronic, shallow forms of ulceration that have been described by such names as "corroding ulcer," "ulcus rotundum simplex," "ulcus serpiginosum," etc.

Such ulcers have slightly raised, sharply cut, sinuous edges, with a comparatively smooth base, irregularly studded with small, imperfectly formed granulations which in places have a florid and almost healthy appearance. A thin parchment-like layer of cancerous growth generally underlies the affected area, which consists of solid ingrowths of epidermoidal cells devoid of "nests." In a case of this kind that I investigated, the disease differed in no essential feature from "rodent ulcer."

The term "corroding ulcer" was first applied to chronic ulcerative disease of the os uteri by the brothers Clarke, who first clearly recognized the condition. They thus designated a slowly spreading, superficial form of intractable ulceration, which gradually involved the whole portio, and eventually destroyed it. The duration of the disease is often ten years or upwards, and the patients affected are generally over forty; thus in its clinical aspect it precisely resembles "rodent ulcer"; but no anatomical signs of cancer were noticeable in connection with it. Very few specimens of this rare affection have hitherto been submitted to careful histological examination; in a typical example recorded by J. Williams no cancer structures were detected. Too much importance need not be attached to a few negative indications of this kind, since the epithelial elements in rodent ulcer are often scanty and the small round-celled infiltration is very abundant; hence, long after Jacob had differentiated "rodent ulcer" as a clinical entity, it was nevertheless classed as a non-cancerous disease. Moreover, instances of tuberculous ulceration of the uterus, especially those of the lupoid type, have no doubt often been described as "corroding ulcer." As to whether any form of ulcerative disease answering to the description of "corroding ulcer" ever occurs in the uterus, as a consequence of local malnutrition dependent upon obliterative arteritis, etc.—as Beuttner, J. Williams, and others maintain—I am certainly sceptical.

Endothelial Cancer.

Only a very few instances of uterine endotheliomata have hitherto been recorded (Braetz, Amann, and others). They are very prone to disseminate. In Braetz's case, the disease presented as a bleeding, papillated tumor, projecting from the posterior lip of the os uteri, the patient being a girl of eighteen.

Inflammation, Ulceration, Retrogression, Spontaneous Cure.

Cancerous neoplasms, once formed, live and are nourished like normal parts of the body; yet they, in return for the nutriment thus supplied, contribute nothing serviceable. Nerveless, functionless, and redundant, their relationship to the rest of the organism differs but little from that of parasitism.

The biology of cancers, like that of normal parts, is conditioned mainly by the inherent properties of their constituent cells, and, in a less degree, by their blood supply. Hence the same elementary pathological disturbances may be witnessed in them as in the affected part itself—*e.g.*, congestion, inflammation, suppuration, gangrene, ulceration, and the degenerative metamorphoses. That long-continued augmentation of the blood supply may accelerate the growth of cancers, and diminished blood supply retard it, is, I think, indisputable. Cases of marked exacerbation of mammary cancers, consequent on pregnancy, traumata, and various irritants, are examples of the former effect; while many very chronic forms of the disease are probably largely dependent upon the latter. I am, however, far from believing that most of the striking irregularities in the rate of growth of cancers can be accounted for by circulatory disturbances. The inherent properties of the neoplastic cells themselves here play the leading part.

The most frequent anatomical cause of *congestion* and *inflammation* of cancers is obstruction of their venous circulation, which, as I have previously mentioned, so often happens during the process of their growth. Cancers are, however, less frequently subject to acute inflammation than might *à priori* be expected. When this does occur, not only the neoplasm itself, but also its immediate surroundings may be affected. Such attacks, which are mostly of septic origin, often greatly accelerate the progress of the disease. Subacute inflammations are commoner than the acute ones. Cohnheim believes that inflammatory conditions of the surrounding tissues weaken their capacity for resistance, and so favor the spread of the disease. Inflammation of cancer may terminate in resolution, suppuration, or gangrene.

Suppuration is rare, but it undoubtedly does occur.

Habermaas relates a curious case, in which the breast was amputated for a tumor—accompanied by enlarged axillary glands—which was believed to be tuberculous. On examination of the part, after removal, this diagnosis appeared to be correct, for there was revealed a pus-containing cavity, surrounded by caseous-looking masses.

Histologically examined, however, these proved to be not tuberculous but cancerous.

Gross mentions the case of a woman, whose breast he amputated for a cancerous tumor the size of a hen's egg. On section of the growth after removal, he found in it an abscess full of greenish pus.

Mammary cancers are sometimes found associated with galactocele, as in cases reported by Wood and Villar.

A more frequent ending than suppuration is *gangrene.* This is generally only partial (necrosis); but exceptionally the whole neoplasm may fall into a state of slough, as in cases recorded by Nunn, Broca, and Warren. Ulcerated cancers are more prone to gangrene than others. Sometimes the sphacelus is determined by injury; but usually there is no obvious cause. Obliteration of the veins is its chief determining factor; hence it is generally of the moist kind, but the dry form is not unknown. Gangrene is always a harmful complication; severe local inflammation and pain attend it, together with profuse fetid discharge, pyrexia, and much constitutional disturbance; and the danger from sepsis is very great. Gangrene may be followed by almost complete cicatrization; but, as the disease is never entirely destroyed, recurrence is inevitable—at any rate, I cannot cite a single instance of cure by gangrene.

I am indebted to Dr. Richmond, of Warrington, for the following account of a case in which a cancerous breast separated by sloughing, consequent on erysipelas:

> A single woman, aged 45, had scirrhous cancer of the left breast and cancerous glands in the axilla. While waiting for extirpation, a sharp attack of erysipelas supervened, involving the diseased mamma, etc. In consequence of this, the diseased breast sloughed clean away, leaving a healthy granulating surface which rapidly cicatrized. There was no return of the disease in this locality, but the undestroyed part in the axilla spread rapidly, and the patient died soon afterwards, with symptoms of internal dissemination.

Billroth has reported an instance in which a mammary cancer of seven years' duration, and the size of an apple, exfoliated spontaneously by dry gangrene, the wound cicatrizing rapidly. When shown at the Berlin Medical Society, shortly afterwards, the cicatrix was quite sound, but its edges were raised and hard.

Like their physiological prototypes of the mamma, sebaceous glands, and epidermis, the cells of breast cancers are short-lived. Hardly ever can one examine a cancerous tumor without discovering some of its cells in *fatty degeneration*, and this eventually ends in their complete disintegration. Such conditions have little or nothing to do with circulatory disturbances; they occur as regular stages in the evolution of the disease, owing to molecular changes inherent to the cells themselves. To this cause we must attribute the tendency of mammary cancers to spontaneous *ulceration*, at a certain stage of their development; which may begin, as Hunter pointed out, either superficially or deeply. In the former circumstance the growing tumor becomes adherent to the overlying skin, which gets thinned and excoriated, and eventually yields, leaving the surface of the neoplasm exposed, and this consequently ulcerates; in the latter, the changes leading to ulceration begin in the substance of the neoplasm, and open outwards. Ulceration once started usually tends to spread indefinitely; yet a cancerous neoplasm is never completely destroyed in this way, for the disease progresses faster than the ulcerative process. Many mammary cancers never ulcerate; this was the case in twelve of the forty-three fatal cases under my observation. Ulceration rarely supervenes until a comparatively advanced stage of the disease.

The *typical ulcer* of mammary cancer presents as an irregularly rounded, excavated, crater-like cavity, with hard, raised, swollen, craggy edges, which are usually everted; and to these edges the surrounding skin is always adherent. Dirty yellowish, sloughy shreds cover its surface; beneath which are undulating projections of the underlying denuded neoplasm, covered here and there with areas of ill-formed granulations. The ulcer is obviously scooped out of the subjacent cancerous growth, hence its hardness; hence also its intimate adhesions with adjacent structures. From the ulcer there exudes a thin, acrid, dirty yellowish ichor, which is often blood-stained; it has a peculiar penetrating and most disagreeable fetid odor. Its contact with the surrounding skin often causes inflammation and even excoriation. In these respects it differs from true pus; it differs also in its composition, which, among other things, comprises necrotic shreds of the growth, degenerated neoplastic cells, leucocytes, altered blood corpuscles, oil globules, granular *débris*, and various *micro-organisms*. Among the latter, Trumpp has met with a peculiar fungus, closely resembling aspergillus niger, but much smaller; and other observers have found various blastomycetes and other microbes.

Cancerous ulcers of long standing often present quite a different aspect to the foregoing; they are shallow, with slightly raised and sinuous edges, the base comparatively smooth, and covered with small granulations, which in places have a florid and almost healthy appearance. A thin parchment-like layer of indurated cancerous tissue underlies the whole affected area, and binds it to the subjacent structures. Such ulcers not infrequently cicatrize more or less extensively, especially at those spots where the progress of ulceration has destroyed the subjacent morbid growth; and they may even remain for long periods in a non-progressive, quiescent state. The conditions underlying these favorable changes are closely allied to those that determine the so-called atrophic form of the disease.

Cancerous ulcers of the breast are liable to bleed; but they seldom bleed freely, and the hemorrhage is easily arrested, if it does not cease spontaneously, as is usually the case. The only really dangerous kind of hemorrhage to which they are liable, is that due to perforation of small arteries; and this is, fortunately, the rarest of all. Nunn has, however, reported an instance of death from capillary hemorrhage, which he explains as due to the impoverished state of the blood preventing coagulation.

Various forms of abnormal *fat formation* in cancerous tumors arise in connection with circulatory disturbances, influencing the metabolism of their cells. Thus, parts where growth is exceedingly active, sometimes exhibit a kind of local adiposis; that is to say, fat globules are separated and deposited in them, which would have been oxidised and removed, but for the local supply of nutritive materials being in excess of metabolism.

Localised fatty degenerations, due to deficient blood supply through venous congestion, inflammation, thrombosis, arteritis, etc., are of frequent occurrence. When the arteries are seriously interfered with, considerable areas of the neoplasm may be affected in this way. In such cases, not only the cells but the stroma also may degenerate, as in the so-called *lipomatous cancers.*

In like manner arise the areas of caseous softening, sometimes seen irregularly scattered throughout cancerous tumors, as in the so-called "caseating cancers." The ultimate fate of such lesions is chiefly dependent upon the subsequent cellular changes; if these go on to complete disintegration, the resulting products may be absorbed and completely disappear, or they may liquefy and form cysts, or caseate and eventually even cretify.

In connection with circulatory defects, mention must be made of the diffuse overgrowth of the fatty capsule of the mamma (*capsular lipoma*), which occasionally accompanies cancer of this and other organs, when the peripheral circulation is interfered with in the progress of the disease.

Ecchymoses and *hemorrhages* into the substance of mammary cancers are not very common. Blood thus effused may be completely absorbed; or, this being incomplete, the residue may cretify or originate a cyst. Cysts thus arising can generally be distinguished by their yellowish lining membrane and straw-colored contents.

Other cysts arise in mammary cancers, owing to degenerative changes affecting their cellular elements; but these are not common, and they seldom attain large size. Owing to the proliferative activity of the epithelia lining the terminal glandular structures, mucoid pseudo-secretion is sometimes produced, which may escape from the nipple or accumulate within the dilated glandular structures, and so form cysts. Cysts containing lactescent butter-like or cheesy matters, of galactocele origin, are occasionally found associated with mammary cancer. Simple involution cysts may also coexist with it. Intracystic papillary growths are, however, hardly ever found in association with acinous mammary cancer. The so-called "hemorrhagic cancers" are not of the acinous variety; they are either tubular duct cancers or villous papillomas: the pseudo-alveolar appearances often noticeable on histological examination, when closely studied, are very different from the alveoli of acinous cancer.

Calcification and *ossification* of the stroma, as previously mentioned, occasionally occur.

The changes produced in mammary cancers by the *colloid*, *myxomatous*, and *atrophic* metamorphoses, constitute special varieties of the disease.

I have before mentioned that the characteristic feature of cancer is its tendency to persist indefinitely, and to increase continuously. Yet indications are not wanting of occasional spontaneous *retardation* and *arrest* of the disease, and even of its *retrogression*; but I cannot cite a single instance of its complete spontaneous cure. Nevertheless, in face of the following facts, I think it would be rash altogether to deny the possibility of such a fortunate occurrence; for, under certain circumstances, the nutrition of cancer cells may be so far arrested as to lead to their complete destruction by disintegration. The extreme chronicity of certain cases of acinous mammary cancer shows that the increase of the disease may sometimes be so exceedingly slow as hardly to be appreciable. Instances of this kind are of more frequent occurrence than is generally believed; and, what is still less appreciated, is that the great majority of such cases are morphologically indistinguishable from ordinary acinous cancer (scirrhus), being neither of the atrophic nor of the colloid variety, although both atrophic and colloid cancers exhibit in a high degree the tendency to chronicity.

Several examples have also been recorded of actively progressive scirrhous cancers—even when ulcerated—having subsequently subsided into quiescent, non-progressive states, with eventual great diminution in size. Nutritive failure leading to degenerative changes in the constituent cells of the neoplasm, and so eventually to their complete destruction by disintegration, seems to be a factor in many cases; but it is probably seldom the chief one. The following are some of the best examples of this *healing tendency* known to me:

CASE I.—In a case reported by Hutchinson, the whole of the right mammary region was occupied by a thin, smooth, parchment-like, glossy scar, which extended backwards beyond the midaxillary line; its edge being slightly elevated, hard, and sinuous, like that of rodent ulcer. Near this large scar-like area were several small, isolated patches of similar appearance. The left mammary region was affected in the same way. Near the anterior border of the left axilla was a subcutaneous nodule, the size of a hazelnut. This was the only situation in which the growth had any thickness. Nowhere was there even a trace of ulceration. There were a few hard glands in each axilla, none of them larger than horse-beans.

The disease began as a hard tumor in the right breast thirteen years ago, and it only subsequently invaded the left breast. Never at any stage had it ulcerated. The patient consulted Mr. Hutchinson on account of pulmonary complication of recent development, which was thought to be due to fluid in the right pleura. After the chest had been tapped several times without any fluid being discovered, it became evident that the dulness was due to intrathoracic solid growth. The patient died about two months later from this cause; but there was no necropsy.

CASE II.—A healthy-looking, childless, married woman, aged 33, under Bryant's care, had an ulcerated cancerous tumor of the right breast, of stony hardness, and firmly fixed to the pectoral muscle. The tumor was first noticed six years ago; and ulceration began four years ago. The ulcer was the size of the palm of the hand—its edges were nodular and crumbly. The axillary glands were enlarged and hard. Operative interference was declined. Fifteen months later the tumor was obviously smaller and harder; and several pieces—the size of nuts—had shed from its edge. Six months later it had still further diminished, and much of the original tumor had crumbled away. Some discrete cancerous tubercles now appeared in the adjacent skin over the sternum. In the course of the next year the tumor continued to contract and to throw off pieces. The cutaneous tubercles notably diminished, and the axillary glands got smaller and harder. Two years later the ulcer had almost completely cicatrized—a puckered linear scar was all that remained, in which were a few small hard nodules. The tubercles in the adjacent skin had completely disappeared. A year later all that remained of the original disease was a single nodule, the size of a hazelnut, in the scar. The axillary glands were hardly perceptible. The patient's general health was unimpaired. One and a half years later she again came under observation; during this interval several fresh tubercles had appeared in the skin near the cicatrix, and had subsequently disappeared, so that only two small ones now remained. The patient considered herself quite well. She died five and a half years later of some pulmonary complication, without any obvious increase of the local disease having taken place. Altogether the disease had lasted for nearly nineteen years.

The two following somewhat similar cases, by Broca, are also of much interest:

Case III.—A woman, aged 69, died in hospital with secondary cancer of the liver. She was admitted with extensive chronic ulceration of the mammary region, which had supervened on hard cancer of the breast of many years' duration. The ulcer was shallow; its edges were but slightly raised, and it had commenced to cicatrize in several places. On micoscopical examination of the part after death it was found that the whole of the cancerous growth had been destroyed by ulceration, except a single nodule, the size of a hazelnut, near the centre of the ulcer.

Case IV.—A lady, when first seen, had an irregular scar in the mammary region, in connection with which there was a small hard cancerous nodule of some months' growth. She said that fifteen years previously she first noticed a tumor in her breast, which subsequently ulcerated, and after a time healed up without any operation ever having been done. Some time afterwards, however, a fresh growth appeared in the cicatrix, which later on ulcerated, but again the ulcer healed spontaneously, after which the present recurrence set in. She refused operative treatment. The disease subsequently progressed so rapidly that she died of it a few months later.

Some instances of retrogression of the local disease, as in the two following cases by Billroth and Walshe, coincide with its outbreak in remote parts of the body. These seem greatly to have impressed the old surgeons, who erroneously regarded them as true metastases, which term they henceforth applied to all systemic disseminations.

Case V.—A woman, aged 40, had an infiltrating cancerous tumor of the left breast, the size of an apple, but refused operation. One year later she again came under treatment with paraplegia due to dissemination of the disease in the vertebræ. The former tumor with its surrounding infiltration had completely disappeared; in its place nothing remained but a flat, indurated, superficial scar, which was slightly excoriated.

Case VI.—A very cachectic woman, with non-ulcerated, hard cancer of the breast of two years' duration, was seized with violent cephalalgia, followed by apoplectic symptoms with hemiplegia. At about the time of this attack the mammary tumor notably diminished; and when she died, ten weeks later, it had almost completely disappeared. The necropsy revealed a cancerous tumor the size of a nut in the brain.

In the next case, by Paget, subsidence of the cancerous disease coincided with the active progress of pulmonary tubercle.

Case VII.—The patient was only 25 years old, yet she had a large, hard cancerous tumor of the breast. The disease had progressed very rapidly, its total duration being only three months. The overlying skin and nipple were invaded. The axillary glands were enlarged and hard. The breast was amputated, when the swelling of the axillary glands subsided. Six months after this operation there was recurrence in the mammary region and in the axilla. In the former situation the disease made rapid progress; numerous tubercles formed in its vicinity, which coalesced and eventually ulcerated. Thus it progressed for a year when the ulcer began to cicatrize, and in the course of six months it had almost completely healed. The axillary disease also subsided, one hard lump alone remaining of what had been a large cluster of hard glands. Meanwhile, however, the patient had emaciated and lost strength, and she died about two years after the operation, and six months after the cancer had so nearly healed, of tuberculosis of both lungs. On careful examination of the mammary region after death, a thin, flattened, nodular *plaque* of extremely hard and dense cancer, was found beneath the old scar, binding it to the pectoral muscle. In the axilla was a single hard cancerous gland; and the liver contained several equally hard growths.

Sigg and others have met with similar cases.

Perrion has seen mammary cancer subside, after an operation for goitre, followed by much suppuration; and Jahr has reported regression of mammary sarcoma after artificially induced delivery.

Several instances of these "retrogressing cancers" have been reported in connection with the uterus, among others by Senger, Rokitansky, Klob, and Scanzoni, but no well-substantiated example of spontaneous cure is known to me. Rokitansky's case of alleged cure by sloughing and ulceration, with the subsequent formation of a funnel-shaped scar, is by no means convincing. Téallier has often noticed retardation of uterine cancer during lactation.

In cases of intraabdominal malignant disease, Bidwell and others have observed marked amelioration after simple exploratory laparotomy. Beatson's cases of regression of mammary cancer after oöphorectomy, evidently belong to this category. Similar results have ensued after thyroid medication, tuberculin injections, and injections with the toxins of erysipelas.

Lastly, it remains for me to mention that in the penultimate stage of the cancerous cachexia and in other exhaustive illnesses, cancerous growths often become stationary, and even appear to wither and dry up shortly before death.

CANCER.

(SYMPTOMATOLOGY AND TREATMENT.)

BY

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NEW YORK.

CANCER.

SYMPTOMATOLOGY AND TREATMENT.

GENERAL CONSIDERATIONS.

Diagnosis.

THE ability to diagnosticate malignant tumors cannot be fully acquired from books. There is no department in surgery in which there is greater need of large clinical experience and well-trained powers of observation. In every case of suspected cancer a careful clinical history should be obtained before attempting any diagnosis. This simple rule will enable the practitioner to avoid many errors in diagnosis. There are some facts in the clinical history which are of special importance and which should stand out with a certain degree of prominence. Among these may be mentioned hereditary influence, the anatomical situation of the tumor, its duration, and the rapidity of its growth. In determining the duration of a tumor, one should always bear in mind that a frequent source of error is due to the fact that the tumor has often existed a considerable time before it was first noticed by the patient. The patient should be carefully questioned as to the size of the tumor when first noticed. By comparing this with the size of the tumor at the time of the examination, one is able to determine with a fair degree of accuracy its rapidity of growth. The situation of the tumor is often of great significance, and here it is important to study not only the anatomical situation at the time of observation, but to make careful inquiry in regard to the exact place in which the tumor originated, or was first noticed. Not infrequently the patient consults the surgeon for a tumor of the neck, and only by careful inquiry does he elicit the fact that a small warty growth or ulcerated area had been removed from the lip or tongue. This is a most important fact, for it at once enables him to differentiate between a primary lymphosarcoma of the neck and a secondary involvement of the glands after a primary epithelioma of the lip or tongue. I was once called to see a large fungating sarcoma in the groin which was supposed to be a primary tumor. The patient denied ever having had any swelling in the leg or foot, but on more careful inquiry it was found that, about two years before, he had had a small ulcerated area upon the ball of his foot caused by irritation from a projecting nail in the shoe. This place at times became apparently healed and at other times discharged slightly; an indurated area about the size of a silver quarter remained, but gave such slight symptoms that the patient never connected it with the trouble in the groin. He soon died of general metastases, and on excision of the area in the ball of the foot it was found to be a pigmented sarcoma, the starting-point of the entire trouble.

The relation of the tumor to the surrounding tissues is a point upon which too much stress cannot be laid. It should be ascertained whether it is adherent to the bony structures, to the muscles, and especially to the overlying skin.

The size of a tumor and with this the rapidity of growth will often throw important light upon the diagnosis. Pain and tenderness, though not so important as many writers would have us believe, should, however, never be forgotten. While in many cases of malignant disease, especially in its early stages, pain may be entirely absent, there are often cases in which, although present to but a slight degree, its peculiar character nevertheless is almost pathognomonic. In the larger proportion of cases, however, the element of pain is of such uncertain value that great weight cannot be attached to it. Senn states that sarcoma as a rule causes less pain than carcinoma, and he believes that "adenoma of the breast causes more suffering than does carcinoma in the same organ and of the same size."

Personally I would regard pain as of greater significance in recurrent cancer than in primary malignant disease, for the reason that in many cases I have seen the patient base her suspicion of a recurrence upon a peculiar "stinging" pain with which she had become familiar during the existence of the primary tumor, and in every case almost without exception the subsequent history has shown that the patient's suspicions were well founded. Even when the patient does not suspect a recurrence, but complains of these peculiar pains, the physician himself should always be on the lookout for a return and should insist upon the importance of frequent examinations. Sarcoma not infrequently may reach an advanced stage with little or no pain. On the other hand, depending largely upon the anatomical situation, it may be the most painful of tumors. I have never seen any carcinoma so painful as a sarcoma of the vertebra or of the orbit.

Tenderness.—In tenderness we have a most important diagnostic sign. This alone, in many cases, will enable us to distinguish a malignant tumor from an inflammatory swelling. While most malignant tumors probably have a slight degree of tenderness, yet, as compared with inflammatory swelling, tenderness may be said to be practically absent in most malignant tumors.

In making the diagnosis of malignant tumor the physician should not only obtain a careful clinical history of the tumor, but a clinical history of the patient himself; he should inquire into his general health, his mode of living, his habits of life, and in addition to this should make a thorough physical examination. The age of the patient should always be carefully noted, for in many cases this alone will either rule out the diagnosis of malignant disease or render it extremely improbable. The general appearance of the patient, in cases of advanced malignant disease, is often of considerable diagnostic value, although when the disease has thus far advanced, diagnosis is of little value to the patient. Loss of weight, especially if considerable in amount and constant, is of much significance. The importance of a careful physical examination of not only the locality of the tumor but of the entire body is at once seen when the question of operative treatment is considered. Not infrequently the surgeon is consulted with reference to the removal of a tumor of moderate size and, from local appearance, entirely removable by operation. If the examination be hurriedly conducted and the general physical examination be overlooked, the operation is performed, and not infrequently it is found later that the patient was already suffering from deposits in the lung, liver, or other regions, a condition which would have been revealed by a careful examination prior to operation. The examination of the tumor itself should be conducted in a thorough, systematic way; its color should be carefully noted; its size, whether protuberant or not; the condition of the overlying skin, whether thickened and adherent to the tumor, or thinned out to a serosa-like membrane; whether ulceration be present or not, and if present, the size and character of the same, as well as the amount and character of the discharge; the presence or absence of induration of the edges should also be noted. As regards the substance of the tumor itself, one should note its shape, whether smooth and symmetrical or irregular with numerous tuberosities. It should be very carefully examined as to its consistence, whether it be firm and hard or elastic and semi-fluctuating. Of all methods of diagnosis, palpation or tactile examination is the most important; by means of this we are enabled to determine the consistence of the tumor, its mobility, its relation to the surrounding tissues, the presence or absence of pulsation, tenderness, crepitation. Mobility is of great diagnostic value and will oftentimes enable one to differentiate between sarcoma and carcinoma, or carcinoma and a benign tumor. If the tumor is bound down or held firmly in its position, this point will have due weight in favor of the diagnosis of carcinoma, and if carcinoma the extent of these adhesions or immobility will be an important factor in enabling one to determine the question as to whether the tumor can be successfully removed by operation or, if inoperable, the probable duration of the disease.

Prognosis.

If the diagnosis of cancer has been made the question that confronts the physician is whether or not to inform the patient of the character of the disease. I believe that in most instances it will prove the better plan to keep the truth from the patient or at least to tell the patient only half truths. There are persons, no doubt, who insist on knowing the real facts and who would probably be the better for being told them. Yet these are the exceptions. As a rule if the patient is told the disease is cancer as soon as the diagnosis is made, the mental depression resulting will not only hasten death but will greatly aggravate the suffering that comes from the disease itself.

If an operation is to be performed, it is especially desirable to give the patient that most valuable help that springs from the hope and belief in a final cure, and if we first state that the trouble is cancer, the popular ideas as to the incurability of cancer are so well fixed that we at once destroy all hope of a favorable outcome.

The nearest friends and relations of the patient should always be told the exact condition: not only the nature of the disease but the dangers attending an operation and the chances of final cure in the event of the operation proving successful. What has been said about keeping the diagnosis from the patient applies more especially to the early stages of the disease. The truth always or nearly always comes to the patient in the course of time, but so slowly and imperceptibly that the "jar" that would at first have been so painful, is nearly or entirely lost. The question is always asked, How long will the patient live? The more we see of the clinical side of malignant disease the more guarded will be our answers. I have known a patient with cancer of the breast of two years' duration, and at that time considered inoperable, live eight years. There are, however, certain general considerations that serve to help us in estimating the duration of life. First among these should be mentioned locality. A malignant tumor situated in a highly vascular region, *e.g.*, the tonsil or tongue, will almost certainly destroy life in a comparatively short time, often less than a year and seldom longer than two.

While a superficial epithelioma of the face may increase so slowly that the fatal issue is postponed for twenty or thirty years, cancer of the orbit is almost always speedily fatal, and the same is true of periosteal sarcomata of the long bones.

Much knowledge as to the future course of the disease may be gained from a careful study of the previous history, the rate of progress, and the presence or absence of early glandular involvement.

The *age* of the patient has a most important bearing upon the prognosis. It may be stated as a general rule: the younger the patient, especially if the tumor be carcinoma, the more rapid the course.

If the patient be beyond seventy years of age, the progress may be exceedingly slow. I once had under my care at the New York Cancer Hospital a woman aged ninety-four years with a cancer of the breast of eight years' duration. I watched the tumor for nearly two years and its change in size was hardly perceptible. The patient herself suffered little in general health and seemed quite as likely to die from some other trouble or from old age as from the cancer.

The early involvement of the lymphatics of the skin renders the prognosis much worse. The presence of small isolated deposits in the skin in a case of cancer of the breast is evidence that operation will be of little avail and that the disease will progress rapidly.

If general dissemination has already occurred, as shown by metastatic deposits, it is needless to say the prognosis is hopelessly bad, and no treatment other than palliative is to be considered.

If the tumor be pigmented (melanotic) the prognosis is almost alsolutely bad, there being very few cases recorded of cure of melanotic neoplasms.

Treatment.

General Treatment.

It would be of little interest to mention the various drugs that have been used in the treatment of cancer, and which had been supposed to have some kind of an inhibitory action upon the disease. Most of these remedies have been in favor for a time and then have fallen into disrepute. There is no inherent or *a-priori* reason why certain drugs should not have a retarding influence upon the development of a malignant tumor, especially if such tumors be due, as many of us believe, to an infectious agent; and even admitting that such a medicinal agent has not yet been found, we should not deny the possibility of its existence and assume such attitude of dogmatic scepticism that would deny it a fair trial if discovered.

Senn states that "no kind of internal medication has any influence whatever in limiting tumor growth, much less in causing the disappearance of a tumor." This statement, while true in a general way, is not in harmony with the fact that there are well-authenticated cases of sarcoma, especially of the skin, in which the disease has been clearly retarded by the use of large doses of arsenic; and further, there are well-authenticated cases of not only sarcoma but of carcinoma that have shown decided improvement under mercurials and the iodides.

Senn explains the fact that mercurial preparations at one time enjoyed such favor among the most influential physicians by stating that "gummata diagnosed as carcinoma disappeared under the treatment, and the results thus obtained gave the remedy its great reputation." To my mind this explanation is too superficial, and is not sufficient, for it clearly assumes a lack of clinical knowledge of malignant disease hardly consistent with what we know of the leaders of the profession at this period.

I have myself seen a case of carcinoma of the breast show such marked improvement under mercurial treatment combined with large doses of the iodide of potassium that it was believed to be a tumor of syphilitic origin. The improvement finally ceased, the tumor was removed and proved to be a typical carcinoma. A similar action has been reported in cases of sarcoma; I have observed two such; hence, while we may safely say that up to the present time we know of no internal remedy that will cause a malignant tumor to disappear, there are certain things that occasionally have a retarding influence upon the growth of the tumor. Among these things should be mentioned arsenic, mercury, the iodides, and possibly protonuclein. The great difficulty in estimating the true value of any medicinal agent as a preventive against recurrence after operation is that it is impossible for one observer to treat systematically a sufficiently large number of cases and to keep them under observation long enough to permit him to draw any positive conclusions. It is impossible to remedy the defect by combining the cases of a number of men, because no two men believe in and carry out the same after-treatment.

Local Treatment.

This includes both operative treatment and removal by caustics, electrolysis, parenchymatous injections, galvanopuncture, or ligature, and cutting off the blood supply. The injection of toxins produces both a local and systemic action, but is of value chiefly in sarcoma, and is referred to at length in the article on that subject.

Ligature of Arteries.

Ligature of the arteries giving nutrition to the tumor is said to have been introduced by Harvey in 1651. It has been much employed in benign tumors of the thyroid. Ligature of the carotid for malignant tumors of the pharynx has been tried in many cases, but in most cases with temporary benefit only.

R. H. M. Dawbarn, of New York, has originated a method of dealing with inoperable malignant tumors in regions deriving their blood supply from the external carotid arteries, which he designates as "excision of the external carotid arteries." Attempts to "starve" malignant tumors by cutting off the arterial supply had previously been made, but never systematically. Four years ago J. D. Bryant, of New York, reported before the New York Surgical Society a case of inoperable nasopharyngeal sarcoma which apparently disappeared after ligation of both external carotid arteries, the patient remaining well nearly ten years afterwards.

Bryant tried the method on a number of other similar cases, but the results were always confined to temporary shrinkage of the tumor. Dawbarn, reasoning from these results that the first case was successful because there happened to be present in this case poor anastomotic connections, and that the other cases were improved at first, but later became worse as soon as anastomosis developed, conceived the idea of *excising* the carotids.

In a recent personal communication Dr. Dawbarn informs me he has carried out this procedure eleven times: in five patients on both sides and in one patient on one side, the opposite artery in this case being simply tied. He classes these, correctly I think, as eleven operations. Ligature of the external carotid is of itself a dangerous operation and should seldom if ever be performed on both sides on the same day. Much less should double excision be performed. Two other operations by the same method have been performed by Dr. J. Chalmers Da Costa, of Philadelphia. The immediate results were remarkably good, neither patient dying from the operation.

The mortality following simple ligature of the external carotid is so high that a number of surgeons who were accustomed to tie it preliminary to extensive operations upon the tonsil or pharynx have abandoned it. Cheyne lost one case of secondary hemorrhage on the twenty-fifth day after operation, and in a second case death was indirectly due to ligature of the external carotid.

The results of excision of the carotid certainly would seem to show that his method is a safer procedure than simple ligature, and if subsequent cases confirm this opinion, we undoubtedly have in this method not only a great aid in operations upon malignant tumors in this locality, but we have an increased prospect of freedom from recurrence.

The *final results* in Dawbarn's five cases are uncertain since most of them are comparatively recent; one case is of especial interest and importance. The patient was suffering from a round-celled sarcoma of the nasopharynx. The growth was considered inoperable, and the mixed toxins of erysipelas and bacillus prodigiosus had been tried (thirteen injections) without apparent improvement. Both external carotids were then excised. The growths atrophied strikingly after operation, and Dr. Dawbarn writes that "the patient is still living, and well with his shrunken growth in place." Such a result as this certainly merits further trials in cases of malignant tumors fed by the external carotid. Dawbarn believes that such growths cannot be "starved" by merely ligating the carotids, inasmuch as there are twenty different ways in which anastomosis may occur if the arteries are only tied.

The *technique* of the operation is as follows: "Ligate the external carotid just above its origin. Cut just above, and seize the cut proximal end with stout artery forceps. These hold the vessel as a handle throughout. Working upwards, tie off between two ligatures and divide each branch as reached. When the artery at length disappears into the substance of the parotid gland, use gentle traction on the artery downwards, while *stretching* with a dressing forceps a passage up into the gland. Avoid the knife here, to threaten facial paralysis as little as may be. At length one is able to slip a single ligature about the two terminal branches just above their origin—the internal maxillary, and temporal—and to divide the end of the external carotid."

Parenchymatous Injection.

Many substances have been used as injections for the purpose of destroying the tumor cells. Senn points out that the use of coagulating substances is dangerous especially in a vascular tumor, on account of the possibility of embolism from a detached blood clot. Carbolic acid, perchloride of iron, nitrate of silver, and alcohol have been extensively used.

The treatment of cancer by *injections of alcohol* was first advocated by Schwalbe and Hasse in 1872 and 1873. Hasse described his method and results in a paper read before the German Surgical Congress in 1896 (*Virchow's Archiv*, 1896, Bd. 146, S. 209). Up to that time he had treated twenty cases of cancer of the breast. A detailed report of the cases is not given nor is it stated how long the patients remained well.

Edwin J. Kuh, of Chicago, has recently tried Hasse's method in a number of cases and is an enthusiastic believer in it. Thus far he has had but one successful case, and this can by no means be considered one of definite cure. This case was a cancer of the nasopharynx (sarcoma) considered inoperable. The tumor disappeared under the alcohol injections in the spring of 1897, the case being reported in the Chicago *Medical Recorder*, April, 1897, also in May, 1898. At the time of the last report it was stated that in November, 1897, an enlarged gland had appeared below the angle of the jaw, and by February, 1898, it had become two or three times its original size. It is fair to conclude that the enlargement was due to a glandular recurrence. Kuh states that Hasse has cured fifteen cancers of the breast out of eighteen (*Virchow's Archiv*, 1897, Bd. 149). The theory upon which the curative action is supposed to be based is that the afferent and efferent vessels are obliterated by the action of the alcohol. Hence the injections are not made into the tumor but into the periphery or tissues just outside of the tumor. Kuh advises beginning with a thirty-per-cent. solution of alcohol and gradually increasing up to forty or fifty per cent. The quantities used vary from 2 or 3 c.c. up to 5 or 10 c.c., and the injections are made every three or four days. The injections are attended with considerable pain. The method has been used a number of times by English surgeons, and I have myself employed it in four cases without apparent benefit. Granting that it may be successful in suitable cases, we cannot expect benefit in cases in which glandular involvement has occurred. In other words, the only cases likely to be benefited are the very ones most favorable for operative treatment, and I cannot see any advantage in substituting for the latter a method far more painful and one requiring an extended period of time.

Caustics.

The use of caustics is at present largely confined to irregular practitioners. With the dangers from an operation reduced to a minimum and with freedom from pain during its performance, there is less and less reason for the employment of caustics.

There is no reason to believe that removal by caustics of any kind renders the patient less liable to a recurrence than if the tumor had been removed by a knife. On the other hand, with our increasing knowledge of early glandular involvement—meaning thereby areas beyond the reach of the caustics—there is every reason to suppose that removal with the knife gives the patient a far better chance of final cure.

In small and very superficial epitheliomata of the face, there is no doubt the disease can often be fully and successfully removed by means of caustics. One of the best of these for this purpose is the liquid butter of antimony, which is best applied by means of a glass rod. Chloride of zinc, caustic potash, arsenic, and chromic and nitric acids have been most commonly employed as caustics.

Cataphoresis.

This has been employed by Morton, Massey, and others in malignant tumors, with a certain degree of success.

Carbide of Calcium.

Within the last year some very interesting investigations have been made by Dr. J. H. Etheridge, of Chicago, in the treatment of inoperable cancer of the uterus with carbide of calcium. Inasmuch as the method gives promise of proving of some value as a palliative measure, a somewhat detailed description will be given. The carbide of calcium is a crystalline compound first obtained by Moisson in 1894 by means of an electric furnace generating a temperature of 3,500° C. In the presence of water this compound produces acetylene gas, the new illuminant.

Acetylene, containing C and H, permits the curious fact that by the addition of the proper amount of oxygen pure alcohol can be made. Commercially pure alcohol can thus be made at a cost of four cents per litre.

Acetylene gas is distinctly poisonous when administered to animals in a sufficiently concentrated form. Inhaled in the open air, it is but slightly harmful. The recent experiments of Gréhant, Berthelot, and Moissan show that it is fatally poisonous when present in proportions as high as forty per cent. by volume. One hundred volumes of air dissolve about eighty volumes of acetylene. If any compound of acetylene and hæmoglobin is formed, it is very instable and is not analogous to carboxyhæmoglobin (Brocinet: *Boston Medical and Surgical Journal*, July 30th, 1896). One pint of pure acetylene given rapidly to dogs, guinea-pigs, and other animals caused severe symptoms of poisoning, but the animals recovered when placed in the open air. If given slowly, they did not recover when placed in the open air (Mosso and Ottolenghi: *Riforma medica*, January 23d, 1897). Paralysis of the respiratory function is the toxic effect of this gas.

Recently many reports of explosions of acetylene have been made in current publications. Its explosive power is greater than that of ordinary illuminating gas, but it is not more dangerous when the ordinary precautions are taken. Brass should be avoided in pipes and burners intended for use with acetylene, since it unites with copper to form solid copper acetylene, which explodes violently on percussion or on heating to 200° C. Rosemann states positively that acetylene does not combine with hæmoglobin (*Archiv für experimentelle Pathologie und Pharmakologie,* Vol. XXXI., p. 179). The poisonous action of acetylene, while admitted by all experimenters to exist, is now claimed to have been greatly exaggerated by earlier investigations because of the probable presence of impure gas (Gréhant, Berthelot, Moissan, and Brocinet: *Comptes Rendus de la Société de Biologie,* 1896). Its odor is not unpleasant. To some people it is faintly aromatic. When the carbide of calcium is reduced to the pulverulent state, the gas can still be evolved and ignited.

In the fall of 1896, Etheridge says that he first saw reference made to the use of carbide of calcium in the treatment of uterine cancer in some medical journal. It was contained in about four lines, which stated that some German physician used it in treating cancer of the uterus. Etheridge says he cannot recall the surgeon's name, but disclaims for himself any credit of originality in the use of the remedy.

After determining that one has to deal with uterine carcinoma, the necrotic *débris* is thoroughly removed by curetting under anæsthesia till firm tissue is reached. Hemorrhage from arterial twigs is then checked by the use of the Paquelin cautery. Free irrigation with very hot water is then used to check the oozing, if necessary. It is desirable to have the seat of the operation as dry as possible before using the carbide. Into the cavity, which extends to a greater or less extent up into the body of the uterus, a piece of the carbide about the size of the last phalanx of one's thumb is placed. At once acetylene gas is evolved which quickly fills the entire cavity with a froth, like soap bubbles. The cavity is immediately packed firmly with iodoform gauze. The vagina is packed full of the same material down to its ostium. The patient is then put to bed for three days, when the gauze and the carbide remains are removed and a new piece is used. The carbide remains are simply a grayish clay covering the cavity in the body of the uterus. It can be sponged and irrigated away in a few minutes, dried by sponging, and prepared thus for another application of the carbide. Upon depositing the carbide in the wound, we witness the same bubbling of gas as before. Gauze packing is then used and the patient is permitted to remain three days until the next dressing.

After a series of such applications of the dressings, the ragged, necrotic ulcer is converted into a simple, clean ulcer. It presents a base covered to all appearances with the pinkish-red granulations, destitute of the gray color which characterized its appearance after the second or third dressings. After a few treatments the edges of the cavity begin to draw in, and the area of the crater is diminished. Its appearance impresses one with the idea that it has taken on an entirely healthy character. Further persistence in the use of the carbide is followed by progressive contraction till finally the cavity is entirely obliterated. There is a puckering of the vault of the vagina about the small uterine os that remains, the whole field being covered by healthy pink mucous membrane.

The following are two illustrative cases in which this method of treatment was employed by Dr. Etheridge.

Case I.—Mrs. Y——, aged 69 years. Her last child was born forty-six years ago. She passed the menopause at forty-eight years of age. For twenty-one years she had no bloody vaginal discharge. On December 14th, 1896, she complained that she had had menorrhagia for six months. At first the bloody flow was only at intervals. At the time of her visit it was continuous. Examination revealed about two-thirds of the cervix absent from carcinomatous ulceration. About one-third of the cervix remained uninvaded. Four days later, at the Presbyterian Hospital, a vaginal hysterectomy was begun. A very careful examination under anæsthesia revealed an apparent invasion of the right broad ligament with thickening and some degree of ankylosis of the uterus. All that was done was to curette very thoroughly and burn with the Paquelin cautery. A cavity was left fully two-thirds the size of an ordinary hen's egg. Into this was placed a piece of the carbide of calcium the size of the last joint of the little finger. A large amount of iodoform gauze was packed against the piece of carbide of calcium and the vagina was filled with gauze. In a week, after leaving the first piece of carbide of calcium in four days, a fresh piece was inserted and left in three days. After each treatment, upon the removal of the gauze, the wound was free from necrotic *débris*, hemorrhage, and odor. The cavity left by the curetting was beginning to contract very rapidly. After the removal of each iodoform gauze packing, nothing remained but sand. The third treatment was made ten days later with the same result, namely, the absence of hemorrhage, discharge of necrotic *débris*, and odor, and the contraction of the cavity. These treatments were continued regularly till well along into May, 1897. The cavity produced by the curretting had entirely disappeared, the thickening in the right broad ligament had disappeared, and there had been no discharge nor hemorrhage.

The patient was not seen again until July 30th, 1897. She was still without discharge or hemorrhage. She was seen again the first week in October, 1897, and was in exactly the same condition. She was not seen again until May, 1898. In the mean time she had been remarkably well and strong, performing her accustomed duties that she had been used to for a quarter of a century. Her seventieth birthday was in January of this year. At her last visit in May, she said that she was having an occasional bloody, grumous discharge from the vagina, coming with a sort of gush as though the pent-up fluid, about a drachm in amount, was suddenly released. She said it had an odor like old fish, not like cancer. This discharge had been going on at intervals of a few days for about a month.

We must await developments in this case, for it will not do to pronounce a verdict until at least two years have passed from the date of operation. The vaginal examination, at her last visit, revealed exactly the condition of things that existed one year ago. The vault of the vagina was drawn together like the apex of a cone with an opening up through it, leading to what was probably the remnant of the uterus. Not a particle of solution of continuity was visible.

Etheridge thinks that the claim can be made that no other line of treatment known at the present time would make a patient so comfortable and entirely free from the usual horrors of cancer for a space of a year and a half, as had been used upon this woman, although he does not call the case one of cure of cancer of the uterus.

CASE II.—Patient, aged 53 years, had passed the climacteric seven years. The cervix was entirely absent through carcinomatous ulceration, which had left the body of the uterus a simple shell. She had had hemorrhages for five months before coming under observation. She was emaciating rapidly and losing strength, and was generally septic. Her face presented the cancerous cachexia. After the necrotic *débris* was curetted away, on July 30th, 1897, nothing was left of the uterus but its cortex. Treatment was precisely the same as in Case No. 1. Similar results followed. After about five months the cavity of the ulceration had entirely disappeared by contraction. In February, 1898, she became very ill with a severe chill and pelvic pains. Relief came slowly under opiates and hot fomentations, and on the eleventh day an abscess suddenly discharged through the small opening in the vault of the vagina. She was up and around in a few days. Since then she has, to all appearances, fully regained her strength and color and has gained flesh. In the early part of May of this year examination revealed a total absence of any vaginal solution of continuity. Nothing but pink, healthy mucous membrane was visible. Since the beginning of treatment in July, 1897, there had been neither discharge, odor, nor hemorrhage. The patient is now performing her customary duties just as she did eighteeen months ago.

As to the *modus medendi* of the carbide of calcium, Etheridge has formed as yet no opinion. Bacteriologically, a series of experiments was made, both with the carbide of calcium and with acetylene gas, on several pathogenic bacteria, under the direction of Professor Hektoen, in the laboratory of Rush Medical College, with absolutely negative results. In a few cases an erysipelatous redness of the sound mucous membrane seemed to follow the use of the carbide, which would suggest that it resulted from an escharotic action of the acetylene gas. Whether the acetylene gas destroys the cancer cell by annihilative action, or by chemically changing it, remains to be seen. One thing seems to be certain, and that is that the carbide of calcium at least postpones death and makes carcinoma patients vastly more comfortable while they live than any treatment known to the writer.

Lymph-Gland Extract.

In the *Medical Press* of November 9th, 1898, Herbert Snow, surgeon to the London Cancer Hospital, reports a case of carcinoma of the stomach in a very advanced stage which was temporarily improved by taking "jelloids" of freshly prepared lymph-gland extract. The extract is given in capsules containing four grains, and one to three are taken after each meal. They cause a slight burning pain and slimy evacuations. Snow states that he is now giving the extract in several cases of mammary cancer which have shown considerable improvement. The administration of opium and cocaine, which he regards as the "sheet anchor" of medicinal treatment in all forms of malignant disease, was used in conjunction with the lymph-gland extract. He suggests that the extract would probably be more beneficial if injected into the tumor itself instead of being given internally. His theory as to the explanation of the action of the extract is as follows:

"A carcinoma beginning at the axillary border infects the glands almost immediately, so that these often quickly enlarge far more rapidly than the primary lesion. On the other hand, a scirrhus deposit close to the sternum does not involve axillary-gland enlargement for two or three months later than the preceding. This is partly of course for the reason that the main lymph current proceeds thence to the mediastinal glands and residual thymus.

"But the importance of relative propinquity in determining the period of gland contamination is very marked under many other conditions. Contrast the rapidity of infection by tongue epithelioma with its tardiness in the corresponding lesion of the extremities; or, most of all, in that attending the external genitals of either sex.

Gland deposit in the former ensues within a very few weeks, never exceeding six, usually far within that limit. With epithelioma of the penis or vulva, the inguinal glands commonly escape for a year. With the same on hand or foot, they rarely show deposit for many months. In the one case, we have a copious inrush of nuclear fragments, which bear down all resistance and at once take root. In the other, there must necessarily also from the beginning be a current of protoplasmic particles to the gland; but it is not for a prolonged period of time that these are able to survive and proliferate.

"I think that no one who intelligently collates a number of chronic cancer cases can well doubt *that the lymph glands resist and for a time destroy malignant protoplasm.* Whether this be effected by a phagocytic action of the lymph cells or by some secretion within the organ is doubtful, and is a matter for scientific investigation. To myself, the latter is by far the more likely hypothesis."

I do not believe we can accept without further proof the proposition laid down by Snow that "the lymph glands resist and for a time destroy malignant protoplasm." It seems to me far more rational to believe that the infectious agent, whether it be a cancerous cell or microorganism, remains in the vicinity of the primary focus of disease during a variable period rather than to believe that it is at once carried to the lymphatic glands, where it is supposed to meet with resistance or destruction. We know that it is possible to have a tuberculous lesion of the foot or knee remain localized, and the fact that the inguinal glands escape can be explained better on the hypothesis that the infection is held in restraint by local barriers than that it early reaches the glands and is destroyed by them.

Operation.

The only treatment of cancer that should at present be considered in cases not too far advanced, is excision with the knife, not only of the local disease, but of the neighboring glands with the connecting lymphatics.

The Limitations of Operative Treatment of Cancer.—If cancer is a local disease, as most authorities at present will admit, the question of its curability depends upon the possibility of removing the entire disease before it has invaded the general system. Hence the question of curability is largely an anatomical one, and depends upon our ability, anatomically and surgically, to remove the invaded area. If we were able to make the diagnosis of cancer before the surrounding lymphatic areas are involved, we should be able to cure the patient of the disease in nearly every case. From a clinical standpoint we know that this is impossible, but with our present limitations as regards early diagnosis, and our present methods of operative treatment, we are able to prolong life in many cases and to effect a permanent cure in a sufficiently large proportion to justify us in urging operation in every suitable case. This brings us to a most important part of the subject, namely, the limitations of operative treatment. There is little unanimity among surgeons as to what are operable and what are inoperable cases, and it is most important to lay down a few general rules bearing upon this question. Some surgeons will operate upon only those cases in which there is a very high probability of final success; other surgeons will go to the other extreme, not only operating upon all cases in which there is reasonable prospect of removing the entire disease, but often performing partial operations, leaving behind large infected areas, both local and glandular. Cheyne states that he does not think a patient should be refused operation unless early recurrence is very highly probable, or unless operation means almost certain death and yields a hopeless functional result. His position is stated in the following words:

"If there is no special danger in the operation and the chances of cure are good, as in the case of an ordinary breast cancer, then I would urge the operation and should not enter into any such details with regard to the disease as might frighten the patient. Where the operation is more severe and the probable result is not so good—as, for example, in a breast case with marked adhesions to the muscle—I do not urge the operation; but I tell the patient that I think it is still worth while taking the chance, and I also point out that there is likely to be a good deal of inconvenience after operation in the way of interference with the movements of the arm. Where the immediate danger of the operation is very great, as in the throat cases, but where it still seems anatomically possible to take away the whole disease, the decision must, I think, be left entirely to the patient."

The attitude that Mr. Cheyne assumes is that if, after emphasizing the dangers of the operation, and putting the whole matter before the patient in its worst light, the patient still desires the operation, he is willing to perform it. The great majority of patients with far advanced cancer, he says, when they know the facts prefer to get along as best they can without the operation, while the few who decide to have it performed obtain a prolongation of life or permanent freedom in a small proportion of cases.

Studying this question from all points of view, we must not lose sight of the fact that in operating upon these almost hopeless cases of cancer, the resulting high mortality and small proportion of cures cannot but have the effect upon other and future patients of destroying confidence in all operations for cancer, and thus many who would certainly be benefited by surgical interference will be led to refuse operation.

Operation therefore, in my opinion, should not be advised unless there is a strong probability of being able to remove the entire disease. Partial operations, in which some of the disease is left behind, not only do not prolong life, but in many cases cause the tumor to grow much more rapidly. In some cases it may be of an advantage to remove a foul fungating mass for the sake of the comfort of the patient.

CANCER OF SPECIAL REGIONS.

Cancer of the Breast.

Symptoms.

In the case of a woman consulting a physician in regard to a tumor of the breast, one of the first questions asked should be concerning the patient's age. Many of the cases of carcinoma of the breast that have been reported in medical literature in persons comparatively young have been cases in which the diagnosis was not confirmed by careful pathologists. In the great majority of instances the disease does not appear until after the age of thirty, indeed rarely before the age of thirty-five. Gross gives the average age as forty-eight years. A clinical history of a typical case of carcinoma of the breast will be somewhat as follows:

If the tumor be cancerous the patient will be in middle life, probably between the ages of thirty-five and sixty years; she will be married (in eighty-eight per cent. of cases collected by Gross the women were or had been married); she will state that she first noticed a slight pain in the breast some months before; careful questioning will reveal the fact that this pain was of a peculiar character—a sharp twinge, quickly passing away, and not occurring again for some hours, or days it may be. She at first regarded it as probably rheumatic or neuralgic, and, as is often the case, she may state that occasionally she felt pain of the same character in the arm. It is never a dull, constant, aching pain, especially in the early stages of the disease. Within a few months I have seen a patient whose first symptom was a disagreeable feeling in the right arm. These peculiar pains which I have described occurred first without any known cause. She was treated for neuralgia. Very shortly after that the arm became suddenly swollen without any known cause. Various speculations as to the nature of the swelling or the cause of it were given from time to time, and corresponding remedies were applied by the family physician. The swelling did not disappear and in fact gradually became more marked. A few months later she noticed a hardness and flattening of her right breast, but never associated the condition of the arm with this. I found the breast the seat of an advanced atrophic scirrhous carcinoma, which had given rise to absolutely no symptoms prior to the peculiar sensations and swelling which developed in the arm.

This case shows the great importance, especially in middle-aged women, of making a thorough examination of the breast in all affections of the arm accompanied by pain or swelling. Shield and Gross point out the great importance of a thorough physical examination in all cases of suspected carcinoma, especially if the disease has existed for any length of time. Many of the peculiar pains which are called rheumatic, and are referred to different parts of the body, are unquestionably due to metastases which have already taken place, and the surgeon who, after a cursory examination, proceeds to amputate the breast for an apparently insignificant and easily removable carcinoma performs a task which a thorough examination would have shown him to be useless. Snow has pointed out the fact that in a very large proportion of cases of carcinoma of the breast, especially in those which have existed for one year or more, the bone marrow has become involved.

We must not regard the element of pain as of too great importance, for many cases of cancer of the breast become well advanced without having caused any appreciable pain. Gross states that a carcinoma begins as a small painless nodule. Dennis, however, states that pain is wanting only in exceptional cases. The family history of the patient, and the previous personal history, should be carefully inquired into. The influence of heredity in the causation of malignant disease is discussed in the preceding article, and I need not dwell upon it here. I merely wish to call attention to the fact that it is of undoubted significance. A history of heredity is found in about twenty-one per cent. of all cases; Gross says nine per cent., Williams, twenty-four per cent. A careful inquiry should always be made as to whether or not relatives of the patient have suffered from malignant disease. If there is a history of several near relatives having died of the disease, this fact will have some weight in determining the diagnosis of the case in hand. But it should not be allowed to outweigh the opinion derived from a careful physical examination of the tumor itself. The previous history of the breast itself should be carefully investigated, and inquiry should be made as to whether or not there has been inflammatory trouble or trauma of any kind. Previous inflammatory trouble, or a blow received a short time prior to the development of the tumor, is a fact of still more importance than the family history, for notwithstanding that many refuse to believe that there is any etiological relation between a trauma and a malignant tumor or a chronic inflammatory condition, the clinical fact remains that these conditions are frequently associated with the development of cancer, and although at present the explanation of this relationship may not be satisfactory, the facts must have some weight in making a diagnosis. A history of previous trauma is found in about twelve per cent. of all cases.

Physical Examination.

Compared with a careful examination by the fingers of one familiar with malignant disease, all other means of diagnosis are of small importance. Shield has well said that "it is by this means that the diagnosis of carcinoma in the early stages is generally settled," and he lays considerable stress upon the proper way of conducting the examination, which he describes as follows: "The thorax should be quite uncovered. The patient should recline upon a sofa or an easy-chair; the suspected breast examined with the 'flat' of the fingers, and never only by 'pinching' of portions of breast tissue between the thumb and forefinger. In marked cases of the usual carcinoma, the deposit is as hard as a piece of wood. Its outlines are more obtuse, seldom perfectly rounded, and the surrounding breast tissue is attached to it or moves with it, the greatest hardness being towards the centre. In the early period of the malady, with which we are now especially concerned, the nodule of disease may not be larger than a haricot bean, yet the hardness will usually be very striking and evident." Examination will show a hard "lump," more probably situated near the periphery of the breast.

In addition to the peculiar hardness which is so characteristic of carcinoma, there are certain other features that are but little less important. Among these may be mentioned, first, the fixation of the tumor. There is but little mobility except in very fat persons with loose, flabby breasts, in whom this sign should have little weight. The nipple is retracted in about fifty per cent. of the cases, according to Gross. There may be a slight discharge from the nipple, but this is found in only about seven per cent.

Its relation to the *skin* is another point of great importance. The condition of the skin seen in carcinoma is almost pathognomonic, there being but few conditions that simulate it. This peculiar condition, known as "dimpling of the skin," is caused by the contracting of fibrous tissue lying between the skin and the mammary glands. It is found not only in comparatively superficial carcinomata, but is seen also in nearly all cases of deeply seated cancers. Shield states that in a large proportion of the cases the skin is obviously dimpled, and there is no sign of more vital importance than this. He further adds that the slightest dimpling in the skin of the breast in an elderly woman is a dangerous symptom, which cannot be ignored or neglected by the physician. It should be remembered, however, that there are other conditions besides carcinoma which may more or less closely simulate this dimpling. Among these may be mentioned contractions of the skin due to old abscesses of the breast, and congenital imperfections. The deeper the tumor, with reference to the puckering of the skin, the more certain is it to be carcinoma.

Careful examination of the axilla should always be made; for, although the absence of *enlarged glands* by no means militates against the diagnosis of carcinoma, their presence makes the diagnosis much more probable. The glands will almost always show a peculiar hardness, which is quite characteristic of cancer. One should not, however, lay too much stress upon the presence of enlarged glands, remembering that they may be due to various other conditions—for example, chronic inflammatory affections, tuberculous disease, eczema of the breast, and even innocent tumors, if these have been previously irritated. In the very rare cases of primary syphilitic disease of the nipple, enlarged glands in the axilla are to be found. The patient may give the history of variation in size of the glands in the axilla, stating that they have been very much larger and have subsided. While this at first sight might tend to show that the disease was not cancerous, the change may be due solely to the subsidence of some inflammatory trouble in glands that are actually the seat of malignant disease.

As regards the frequency with which glandular enlargement is found in carcinoma of the breast, statistics vary considerably. Gross has computed it as sixty-four per cent. of all cases. Shield, who has made very careful investigation of the cases at St. George's Hospital, states that enlargement was found in nearly fifty per cent.; but he believes that this estimate is probably far short of the truth, for the reason that in many cases the glands are really involved and yet give no evidence of the fact upon palpation. If the disease has advanced sufficiently far to have involved the skin itself, the diagnosis usually will present no difficulty: The skin is markedly congested, of a reddish or purplish hue, has the characteristic appearance to which the term "pigskin saddle" has frequently and appropriately been applied. If this condition has lasted for any length of time, ulceration usually will have occurred, and a thin acrid discharge will be present. The edges of the ulcerated area are usually slightly elevated and exceedingly hard. In the majority of cases, the symptoms which have already been mentioned are sufficient to enable one to make the diagnosis of carcinoma; but occasionally cases are met with in which exploratory incision is necessary before one can be certain as to the nature of the tumor.

Differential Diagnosis.

The tumors most likely to be mistaken for carcinomata are the fibroadenomata, slowly growing sarcomata, and chronic inflammatory and tuberculous diseases.

Fibroadenomata may usually be differentiated, by the fact that they occur as a rule in younger people, and are much more movable than carcinomata; the peculiar dimpling of the skin is absent, and their development is slower; besides there is no retraction of the nipple. Of 63 cases of fibroadenomatous tumors collected by Shield, 45 occurred before the age of forty, 18 afterward; 21 of the patients were married, 42 were single. Another point of considerable importance is the fact that not infrequently these tumors show great variation in size, sometimes increasing markedly within a short period, and again diminishing as rapidly. In connection with the decrease in size, a discharge of a serous or bloody fluid from the nipple may be noted. The consistence of these tumors differs very much from that of a carcinomatous tumor. In the fibroadenomata, cysts are not infrequently found, and in such cases either fluctuation can be made out by careful palpation or, if not fluctuation, a sense of elasticity may be detected over certain areas. It is true that cystic degeneration may occasionally take place in a carcinomatous tumor, and when this has occurred, the diagnosis may be attended with very great difficulty. The diagnosis of carcinomatous cysts, according to Shield, rests upon the following points: 1. The patients in the recorded cases have usually been adults, from forty to fifty years of age; 2. Cysts have been large, oval or round, and the contents clear, amber-colored, or colloidal; 3. On exploratory incision, either nodules or solid growths have been discovered at one part, or the walls of the cyst have been irregulary thickened and infiltrated.

In spite of these points, we must in candor confess that the diagnosis can rarely be made without an exploratory incision. Personally, I have never seen a carcinomatous cyst of the breast, but a case of epithelioma of the neck well illustrates the difficulty in diagnosticating such conditions.

The patient, a man 55 years of age, had had a swelling in the right side of the neck, situated just behind the angle of the jaw; it was about the size of a hen's egg, firmly fixed, the skin was reddened and more or less infiltrated, and a sense of deep fluctuation could easily be made out on palpation. The swelling had existed for several months, had increased very slowly in size, and was accompanied by moderate pain. On aspiration, a seropurulent fluid was withdrawn, which closely resembled that found in tuberculous disease. Exploratory incision showed a cavity filled with about two ounces of what appeared to be typical caseous pus. The bottom of the cavity extended to the mastoid portion of the temporal bone. An attempt was made to find some portion of denuded bone, the clinical appearance being perfectly typical of tuberculous disease, the walls of the cavity being slightly more thickened than one would expect in tuberculous trouble. A portion was removed, and microscopical examination proved it to be an epithelioma.

Some authorities lay little stress upon the diagnosis between malignant and *non-malignant tumors* of the breast, considering it better to sacrifice the organ for all tumors, whether malignant or benign, believing that even benign tumors, if allowed to remain, very frequently become malignant. Every surgeon of large experience in malignant disease has doubtless seen cases with a history of carcinoma developing from a small and apparently harmless nodule that had existed for many years; but this fact does not, I believe, warrant us in advising the removal of the breast on every occasion when one of these apparently benign tumors has been discovered. By a careful study of these tumors, it is possible in the great majority of cases to differentiate the innocent from the malignant, and I do not believe that we are justified in making it a rule in surgery to remove all tumors of the breast first and to make our diagnosis afterwards. If a tumor is clearly benign, it can be removed without causing any appreciable disfigurement, and the patient will probably remain as free from any further risk as if the breast itself had been removed. It is true that there have been a number of cases recorded of fibroadenomata recurring after operation; but in the majority of these cases it is more than probable that the original diagnosis was incorrect, and that the disease was really sarcomatous. The removal of such tumors, however, should be undertaken with even greater care than the removal of a carcinomatous breast, for the wound healing is far more likely to be attended with complications than if the entire organ is removed, and if suppuration does occur, very troublesome and long-standing sinuses may be developed, which are extremely difficult to heal. This should be borne in mind when making the exploratory incisions which I have advised in certain cases in which the diagnosis could not be settled in any other way. I have seen the removal of a small portion of a tumor of the breast, for diagnostic purposes, cause more trouble to the patient, as well as to the surgeon, than an amputation for carcinoma, for the reason that it is extremely difficult to perfectly control the hemorrhage, and, unless this be done, the oozing will permit small accumulations of blood to form, which may seriously interfere with the wound healing.

Chronic Inflammation.—This condition not infrequently causes much difficulty in diagnosis. The chief points which may enable us to differentiate it from carcinoma are the following: The disease seldom presents such a sharp outline as is found in carcinoma, being less localized; in a considerable number of cases both breasts are affected in chronic mastitis, which is seldom the case with carcinoma. Mastitis occurs most frequently in connection with lactation, while cancer is seldom seen at this time. While the nipple may be somewhat retracted in chronic mastitis, and the axillary glands somewhat enlarged and tender, the dimpling of the skin is absent. Williams attaches much importance to the "presence or absence of pain and *tenderness* on *manipulation*," cancer in the early stage being seldom very painful and but rarely tender. In the early stages of cancer it is not always possible to differentiate the disease from an inflammatory nodule, and in such cases external applications, counter-irritation combined with the administration of mercurials and iodides, have been recommended. If such treatment be undertaken, one cannot too strongly urge the importance of watching the case very closely, and of discontinuing the treatment after a very short trial if no improvement be apparent.

A warning should be given that we cannot always be sure that the disease is non-malignant, even if it does show improvement under the treatment mentioned. The following is an illustrative case of carcinoma of the breast in which marked improvement took place under large doses of iodide of potassium and mercury.

Mrs. K——, aged 38 years. Married eighteen years; no children; seven miscarriages. Well-marked specific history. Two years before there had been a characteristic rash, pain in the bones, sore throat, and hoarseness with temporary loss of voice. The patient was admitted to the New York Cancer Hospital, September 1st, 1895, with a history of having first noticed, fifteen months before, a small indurated spot in the extreme lower portion of the right breast, in the fold between the skin of the breast and the chest wall. This increased slowly and in July, 1895, began to break down and ulcerate. Examination showed an ulcer in the region described, two inches long and about one inch deep, directly in the fold of the skin; its edges were indurated; the ulcer had a foul, sloughing appearance. In view of the specific history, it was thought that possibly it might be of syphilitic origin. She was put upon large doses of potassium iodide, which were gradually increased until she was getting four hundred grains a day. The ulcer soon assumed a more healthy appearance and the induration decidedly diminished. At the end of five weeks' treatment she was so much improved that she went home. After a short time, however, the improvement ceased, and she returned to the hospital. A piece of the tissue was removed under cocaine for microscopical examination, which showed it to be a typical carcinoma. Amputation of the breast was at once performed.

In cases in which the clinical history and the physical signs fail to render the diagnosis certain, I would waste little time with external or internal treatment, relying upon the more certain method of an exploratory incision. Differentiation of carcinoma from sarcoma will be dealt with more fully under the subject of sarcoma. One other condition may occasionally give rise to confusion, and that is keloid; but the history of the swelling appearing after some injury or incision, together with the very slow development, will usually enable us to differentiate it from malignant disease.

UNUSUAL VARIETIES OF MAMMARY CANCER.

Cancer en Cuirasse.

This is not strictly a different form of cancer, but one in which the early involvement of the superficial or skin lymphatics gives rise to a clinical picture quite distinct from that seen in the ordinary form. It is a comparatively rare type, only two examples of it having been seen in one hundred and seventy cases consecutively observed by Williams. Williams, Senn, and in fact most writers, regard the disease as a cutaneous dissemination of an ordinary glandular carcinoma rather than as primary in the skin. Velpeau was the first to describe this form of cancer, and he also differentiated three distinct varieties, one known as "squirrhe disseminé" or miliary carcinosis; a second, in the form of irregularly shaped discs, as "cancer en plaque"; a third, a diffuse infiltration, as "cancer en cuirasse." His opinion that the disease, in certain cases at least, is limited entirely to the skin is not held by modern pathologists, who are all in accord in regarding the disease as primary in the breast, with an early and rapid extension to the cutaneous lymphatics. In one hundred and seventy consecutive cases of mammary cancer Williams observed only two of "squirrhe disseminé," one of which he cites as a typical example:

A woman, weak and emaciated, aged 32 years, presented herself with a hard tumor in the left breast of one month's duration. The overlying skin was adherent and contained an immense number of small cancerous nodules, varying in size from a pea to a pin's head, which were in some cases confluent. The skin of the parts adjacent to the left breast was similarly affected, as well as that of the left axilla. In a few months the opposite breast and the whole integument in front of the chest were similarly infected. No operation was done. She died of asthenia with symptoms of intrathoracic dissemination seven and a half months after the disease was first noticed.

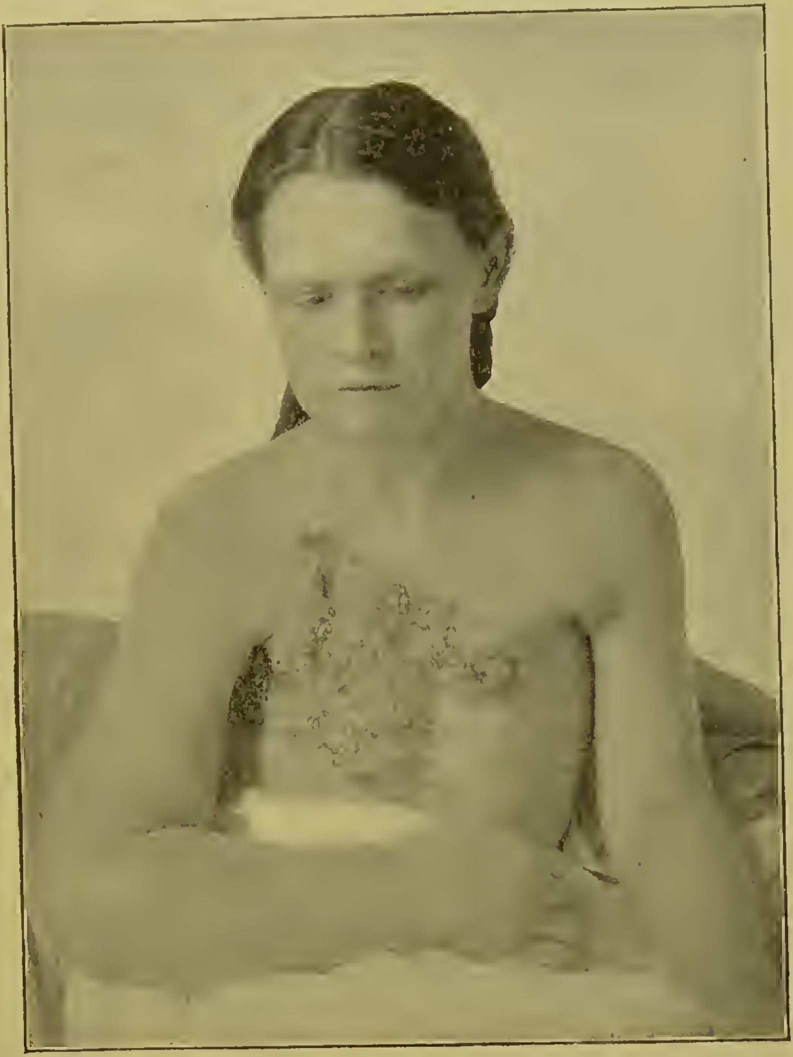

Fig. 1.—Cancer en Cuirasse. (Original.)

Within the last year I have personally observed a case of "squirrhe disseminé," almost identical with that described by Williams. The following is a brief history of the case:

Mrs. R——, age 37, born in Germany, married, the mother of three children; there was no history of heredity. In October, 1897, she received a severe blow in the right breast, caused by striking it against an iron bedstead. Two weeks later she noted a reddish discharge from the nipple. A hard lump was first seen in January, 1898. This rapidly increased in size. When seen by me, April 23d, 1898—less than four months from the time the swelling was first noticed—examination showed the right breast to be twice the size of the left. The entire breast, including the skin, was infiltrated with the disease, the skin infiltrations were mostly about the size of a pea, and in many places they were so numerous as to have become confluent, forming large plaques. These skin infiltrations extended a considerable distance beyond the outline of the breast. The skin was discolored, being reddish in certain portions and purple in others. There was a slight area of ulceration over the most prominent portion of the tumor. The axillary and supraclavicular glands were enlarged, but there was no swelling of the arm. The tumor was moderately fixed to the pectoral muscle. The disease was considered entirely beyond operation. For the next two months, while under observation at the New York Cancer Hospital, the disease progressed with enormous rapidity. New developments would spring up almost daily and in a few weeks the left breast was extensively involved, and the skin infiltrations had extended almost entirely across the chest. The arm did not begin to swell until comparatively late, but the disease ran a very rapid course, death occurring in the early part of October, or about nine months after the time that the tumor was first noticed.

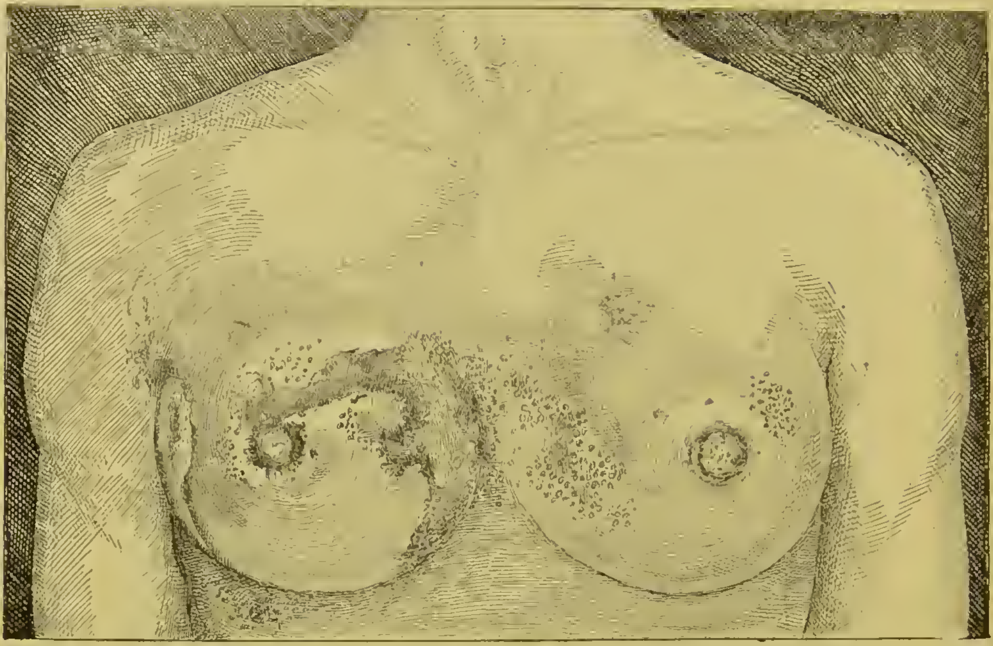

FIG. 2.—Carcinoma of Breast, "squirrhe disseminé," fatal in nine months. (Original.)

In the *diffuse* form, or the typical cancer en cuirasse, the disease begins much more in the manner of an ordinary cancer. There is seldom pain in the beginning, although as the disease progresses the pain often becomes very acute and constant. One of the first things noticed by the patient is often a red or purple indurated spot in the skin over the breast. This is frequently associated with a peculiar stinging or burning feeling, though hardly severe enough to be called pain. Other similar areas soon appear in the neighborhood; these gradually increase, finally coalesce, and in a comparatively short time a large portion of the chest is involved, and the skin of the chest is transformed into a hard leather-like substance, which has given rise to the very appropriate name of cancer en cuirasse. I have observed three cases of this form of cancer, all being women between the ages of forty and fifty, and in all the disease developed slowly and insidiously at first. The skin having once become thoroughly involved, the extension was very rapid. In one case the skin was completely invaded for fully three-quarters of the distance around the thorax, and from the clavicle to the abdomen. The skin, muscle, and fascia were completely destroyed and transformed into this characteristic leather-like covering, which gradually constricted the thorax until it produced constant and agonizing dyspnœa. Three such cases only were observed by Roger Williams in the one hundred and seventy cases alluded to. Gross states that it is met with once in every twenty-two cases; but this estimate is probably too large. The entire duration of the disease in my three cases was about two years. Operation was performed in one case only.

Adenocarcinoma.

Inasmuch as this is a comparatively rare type of cancer, and as it differs somewhat from the latter in its clinical history, the following report of a recently observed case will be of interest:

Miss H——, 33 years old. Family history negative, with the exception that an uncle died of cancer of the knee, following the kick of a horse thirty-four years before. The patient herself had always been well until April, 1896, when she noticed a lump in the right breast. A few weeks later she observed a similar smaller tumor in the left breast. Both grew rapidly in size, and an operation was performed by Dr. H. O. Marcy in July, 1896, four months after the first symptoms were noted. The tumor in the right breast at that time was of the size of an English walnut. The one in the left axilla was smaller. Inasmuch as the tumors were not regarded as malignant, the breast itself was not excised, and the nipples were left intact. A small gland in the right axilla was removed. Two weeks later a hard lump began to appear above the clavicle on the right side. Early in October, the right arm also began to swell. Four weeks later, recurrent nodules were noticed at the site of the cicatrix on the right side. On December 30th, 1896, the patient was referred to me for advice by Dr. Marcy. Examination showed on the right side the entire region of the breast, extending up into the axilla very nearly to the sternal border, completely occupied by hard, irregular masses, which infiltrated the skin and were purple in color. The infiltration extended backwards nearly to the midscapular region. Several larger hard masses were found above the clavicle. Examination of the original tumors by Dr. B. H. Buxton, pathologist to the Cancer Hospital, showed the growth to be an adenocarcinoma. The facts that the patient was only thirty-three years of age, and that the disease ran an almost acute course, make this case one of very great interest. Halsted has recently described a very interesting series of cases of adenocarcinoma (*Annals of Surgery*, November, 1898).

Paget's Disease of the Nipple.

Two cases of Paget's disease of the nipple have come under my observation.

Miss M——, 52 years of age. No history of cancer in the family. She first noticed irritation of the left breast three to four years before. A slight bloody discharge showed itself and this continued up to the time of operation. There was no distinct pain; rather a feeling of discomfort. Physical examination on September 13th, 1897, showed the left breast the site of an ulcer one-quarter by one-half an inch in diameter with indurated edges, and surface of bright-red color; it bled easily. There was no tumor or thickening about the base of the nipple. No enlarged glands could be felt in the axilla. Both breasts were well developed, the patient being moderately stout, weighing one hundred and fifty pounds. Although the disease had extended over such a trifling area, it was thought wise to perform a very radical operation, and the entire breast, together with the axillary glands, was removed. The operation was performed September 13th, 1897. Microscopical examination showed the glands in the axilla were not involved. The structure of the new formation of the nipple proved typical adenocarcinoma. The patient remains well at present, fourteen months after operation.

Mrs. S——, 54 years of age with good family and personal history, consulted me in October, 1896, with an ulcer about the size of silver half-dollar in the region of the left nipple. The nipple itself had been entirely destroyed. The ulcerted area had a bright-red color. There was no tumor to be felt in the breast itself, and the disease seemed entirely confined to the skin. There was only the slightest appreciable induration present in the edges of the ulcerated area. A diagnosis of malignant disease, however, was made, and radical operation was strongly advised. The patient objected to operation, and was lost sight of for one year, after which time she again consulted me. Then the entire breast had become involved with what clinically appeared to be typical carcinoma. The axillary glands were also markedly enlarged. By this time the disease was hopelessly inoperable.

It is not my province to enter into a discussion of the much-vexed question of the etiology of this disease, but the clinical history, the diagnosis, and treatment should be briefly described.

The disease is comparatively rare. Shield states that he was surprised to find from the reports of St. George's Hospital how rare undoubted cases really seem to be. Of 400 cases of carcinomata examined, only 5 of Paget's disease were found. Out of 23 cases collected by Bowlby (Medico-Chirurgical Transactions, Vol. 74), 14 developed cancers; 9 are said to have escaped. It is possible that in some of these 9 the disease would have developed had the patients lived sufficiently long. The duration of the disease in Bowlby's cases in which no tumors appeared, varied between six months and twenty years, while the 14 cases in which cancer finally developed, varied from a few days to twelve years. The age of the patients differs little from that of patients with carcinoma of the breast, the ordinary type of cancer, the youngest of Bowlbey's cases being thirty-six, the oldest sixty-four years of age. Shield states that the affected skin is always infiltrated, and that if a portion of it be pinched between the finger and thumb one can almost always make out the parchment-like thickening. This thickening, while present in both of my own cases, was by no means marked. The ulcerated area itself resembled acute eczema, although the edges were much more sharply defined. In my own cases the ulcers were single. Sometimes, however, they may be multiple, and may extend for a considerable distance beyond the nipple, even beyond the alveoli, covering a large portion of the breast. In all the cases observed by Paget hard cancer of the breast finally developed.

From a very careful study of this disease Shield draws the following conclusions: (1) Paget's disease is rare, and the diagnosis is difficult and not uncommonly erroneous; (2) it is usually, but not certainly, followed by carcinoma of the breast; (3) as is usual with rare maladies, the life experience of one man is hardly sufficient to enable him to strike an average of symptoms and terminations.

Shield's suggestion to substitute the term "superficial carcinoma of the skin" for "Paget's disease" I believe to be a very good one.

As regards the *treatment* of this disease, I am thoroughly convinced that nothing short of a very radical operation—namely, complete removal of the breast and axillary glands—should be performed. Shield states that he has never known a genuine case of Paget's disease truly cured by local remedies. There is little doubt that the majority of the cases reported as having been successfully treated by these remedies are cases of mistaken diagnosis.

Because of the very small extent of the disease, one is tempted to try some milder measure, as, for example, caustics, before resorting to amputation of the breast. Shield strongly advises against any of these half-way measures, and adds that it is probable that excision of the nipple and alveola, or nipple alone, without removal of the breast, is not sufficient to insure the patient against the after formation of cancer, and he cites a very important case in support of his opinion.

The patient, a lady 50 years of age, had had a chronic ulceration on the summit of the left nipple. Palliative treatment was first tried. Finally, the nipple was excised by the advice of an eminent surgeon. Twelve months later, a tumor the size of a marble was found in the upper and inner part of the breast; this proved to be scirrhous. Carcinoma of the breast with a round-celled sarcoma in the submaxillary region occurred in the same patient.

Mrs. M——, aged 53 years, without hereditary history of cancer, was operated upon in the spring of 1894 for carcinoma of the left breast and involvement of the axillary glands. The patient remained well until the fall of 1895, when enlargement was noticed in the left submaxillary gland. This continued to increase until January 1st, 1896, when it had become a tumor three inches in diameter, situated just beneath the angle of the jaw on the left side; it was slightly movable. The patient was treated by her physician, Dr. R. Oliver Phillips, of Yonkers, N. Y., for four weeks with the mixed toxins of erysipelas and bacillus prodigiosus, with the result that the tumor decreased two-thirds in size, and became very movable.

On March 14th, 1896, I operated, under ether anæsthesia. Two spheroidal masses, one three-quarters of an inch the other one inch in diameter, were removed from the deep submaxillary region; both were entirely encapsulated, and on section showed, macroscopically, the typical characteristics of malignant disease. Careful microscopical examination by Drs. E. K. Dunham and B. H. Buxton, pathologists in the New York Cancer Hospital, failed to find anything more than glandular hyperplasia. Careful examination at the time of the operation of the region of the breast, axilla, and supraclavicular triangle showed no evidence of glandular enlargement. The patient's general health was good. In June, 1896, a recurrence took place in the region of the breast and axilla, involving the skin, subcutaneous tissue, and pectoral muscle. In the latter part of July, 1896, I operated, removing the entire diseased area, together with both pectoral muscles. The wound healed without suppuration, the patient making a prompt recovery. Microscopical examination showed the tumor to be a typical scirrhous carcinoma. Shortly after the operation upon the breast a recurrence took place at exactly the site of the first operation, in the submaxillary region, and the tumor grew with great rapidity. I performed another operation in September, 1896, removing an encapsulated tumor, the size of a small egg, with precisely the same characteristics as the first. In view of the macroscopical appearance and the prompt recurrence, I felt convinced that the tumors in this region were more than glandular hyperplasia, and asked for a very careful microscopical report. A large number of sections were made before evidences of sarcoma were discovered. These examinations—by Drs. Dunham and Buxton—showed the growth to be round-celled sarcoma. About a month afterwards a second recurrence took place in the submaxillary region; the tumor grew with greater rapidity than before. The deeper tissues were at this time involved, and further operation was considered useless. At no time were the supraclavicular glands enlarged, and the tumor in the neck had the soft, cystic appearance of a rapidly growing, round-celled sarcoma.

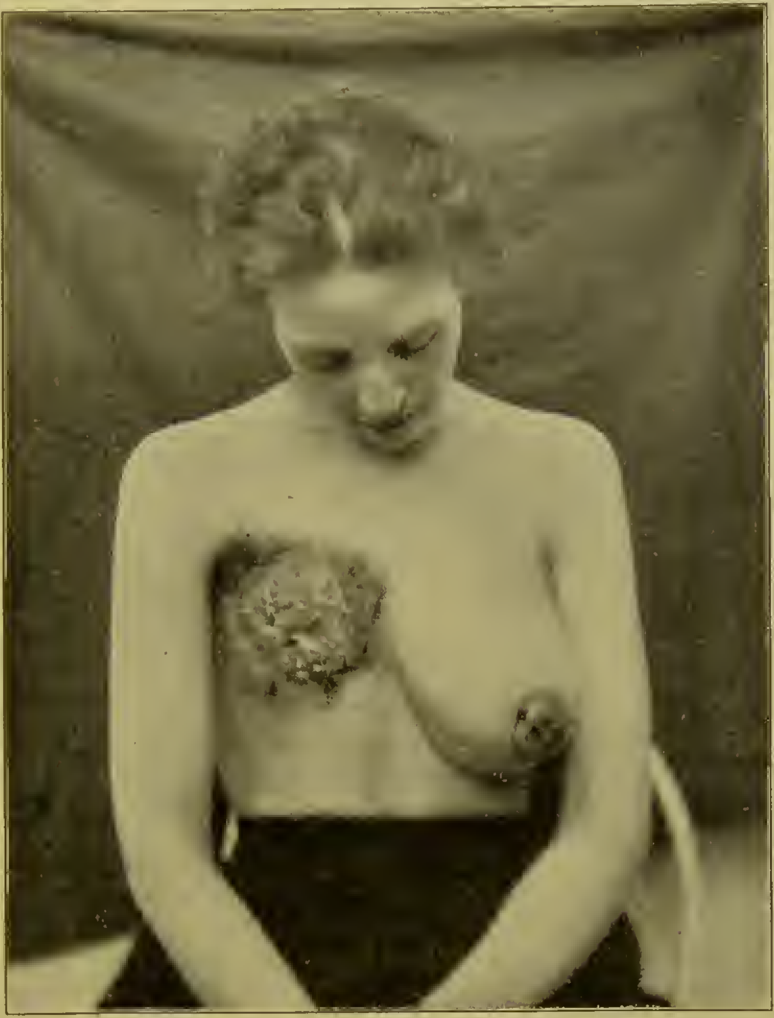

FIG. 3.—Double Carcinoma of the Breast. (Original.)

The subsequent history was briefly as follows: The tumor continued to grow, filling up the entire neck. It became markedly protuberant, and was so soft as to give the appearance of fluctuation, although aspirations failed to reveal the presence of fluid. At no time was there ulceration or sloughing. The growth finally filled the mouth and the neck, making it extremely difficult to speak and still more difficult to swallow. The patient died of exhaustion on March 18th, 1897.

A slight local recurrence of the carcinoma was noticed in the skin; this increased but little, however, and at the time of death was no more than a small infiltration of the skin.

Repeated examinations of the tumors removed from the neck showed no trace whatever of epithelial proliferation; hence this case seems to be one that can be explained only on the theory of two entirely different forms of malignant disease occurring in the same individual.

As examples of the coexistence of mammary cancer with sarcoma elsewhere, Roger Williams was able to collect eleven cases; in eight of these, the sarcoma was found in the other breast, while in three, the sarcoma—the same as in my case—appeared in other regions than the breast.

The accompanying illustration (Fig. 3) shows very well the appearance of a double carcinoma in a woman of forty-two years. No operation was performed as the disease was inoperable when she consulted a surgeon. The progress was rapid.

CASES OF CARCINOMA OF THE BREAST IN THE AGED, ILLUSTRATING THE SLOW PROGRESS OF THE DISEASE AT THIS PERIOD.

Mrs. B——, 77 years of age. Good family history. In 1888 she first noticed a small lump near the nipple of the right breast. This grew slowly in size, and four years later amputation of the breast was performed by Dr. William T. Bull, at St. Luke's Hospital. She remained well for three years, when a local recurrence in the region of the old scar was noticed. There was no glandular involvement. The disease progressed very slowly, and a year later a small gland appeared in the axillary region. There was never any swelling of the arm, and the growth in the breast showed very little appreciable change for nearly two years. Death finally occurred from exhaustion, in the early part of 1898, ten years from the beginning of the disease.

Mrs. M——, 94 years old. Thirty years ago the patient fell, striking the breast on the corner of a bedstead. A tumor developed shortly afterwards. This was removed by caustic paste. She remained well for fifteen years, when there was a recurrence. The disease was removed a second time in a similar manner. Another recurrence followed and the paste was again applied in 1886. Local recurrence followed, but the exact time was not noted. Her condition on April 22d, 1898, showed a mass the size of a hand adhering to the chest wall, with several small nodules infiltrating the skin beyond the main tumor. The whole growth had the appearance of a typical carcinoma. The patient at this time was suffering very greatly from cough and dyspnœa. Moderate cachexia was present.

TREATMENT.

The attempt to remove cancer of the breast by some method of operation dates back to very early times. Earlier methods aimed to remove the entire breast. As to the final results of the very early operations, we have little definite information. Prior to 1870, the medical profession had lost much of the earlier faith in the efficacy of any operation for cancer of the breast, and the surgeons who performed them contented themselves with removing the tumor itself, closing up the wound with as little deformity as possible, and never interfering with the axillary glands. To Moore of London, and Gross of the United States, we are largely indebted for the great advance in the treatment of cancer of the breast. Moore, in 1867, showed the incompleteness and inefficacy of the methods then in vogue, and strongly urged extirpation of the entire organ, and especially of the adjacent skin. Gross, in 1880, practically outlined the complete operation of to-day, advising not only the removal of the entire breast and the axillary glands, but urging dissection of the fascia over the pectoral muscle. Still later, in 1889, Heidenheim, by his very careful and scientific investigations as to the manner in which cancerous cells extend from the original focus of the disease into the neighboring parts, demonstrated the facts many of which Moore and Gross had

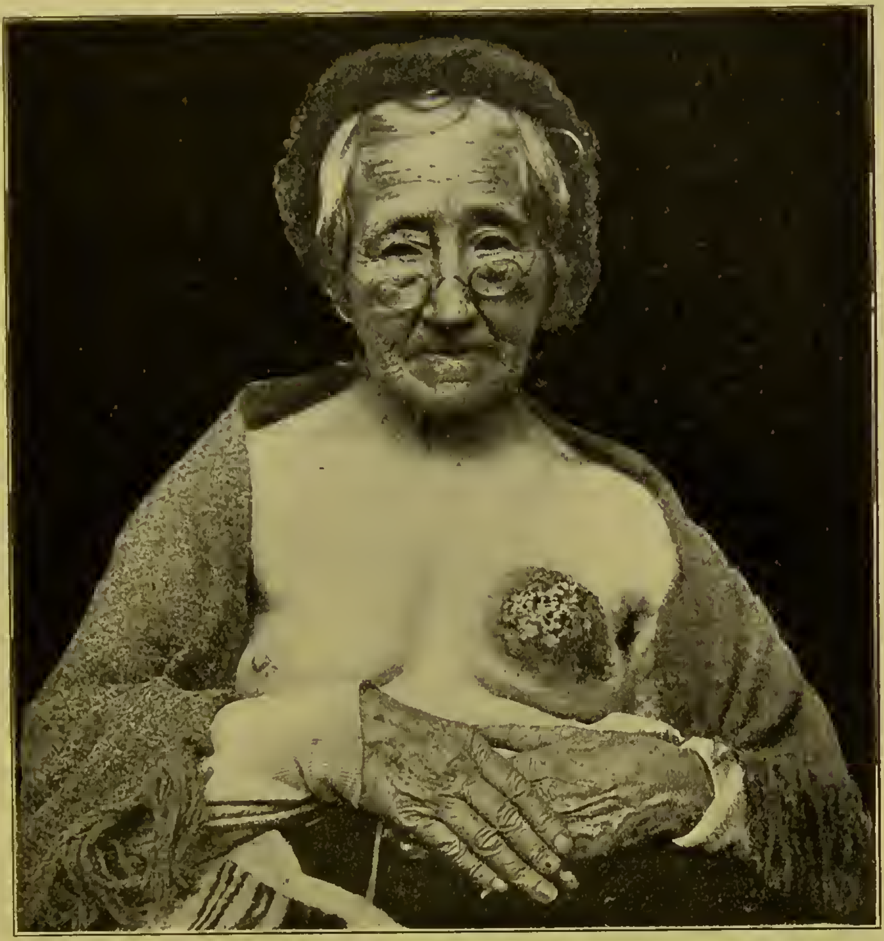

FIG. 4.—Carcinoma of the Breast in a Woman Ninety-four Years Old. (Original.)

already from clinical observations years previously assumed as true. The gist of Heidenheim's results may be summed up in a few words. A cancerous tumor of the breast that has become sufficiently large to be recognized clinically has already scattered its infectious cells throughout the entire breast, the neighboring chain of glands, and in many cases the fascia overlying the pectoral muscle.

Before discussing the different methods of operation at present employed, it is well to take up the question of the possibility of curing cancer by any operation.

The statistics of operations for cancer of the breast have been more accurately and fully worked out than those of cancer in any other locality; hence, at present, we are in a position to state fairly definitely the percentage of cases that are likely to be cured by operation. This does not mean that we can in every case give an accurate prognosis, for we cannot too strongly emphasize the fact that the disease is one liable to the greatest variations, which make it impossible for the surgeon to give any definite time limit in an individual case of cancer of the breast. It is a common belief that, if the surgeon could see all cases in the early stages, a cure would be assured. This idea is by no means true. While in a general way the prognosis is better the earlier the operation is performed, there are cases in which the malignancy is so great that an operation, even if performed as soon as the tumor has become sufficiently large to be noticed by the patient, fails to prevent a speedy recurrence. A good illustration of this is a case observed by the writer two years ago.

The patient was an unmarried woman, 35 years of age, with a small nodule in the left breast, not larger than a hickory nut. This nodule had been noticed about eight weeks, was but slightly painful, and was situated in the upper and outer quadrant, rather deeply located in the substance of the breast. It was not adherent to the skin, and no enlarged glands could be found. The diagnosis of carcinoma was made chiefly upon the single sign of characteristic hardness. A very thorough operation was performed, and all of the axillary glands and fat were carefully removed. In the mass of fat two or three small glands were found that appeared harder than normal. Microscopical examination showed that they were already carcinomatous. In less than six months there was a slight recurrence in the axilla, which was removed by operation. A few months later the arm began to swell, although no tumor was appreciable on palpation. The patient gradually failed in general health, developed signs of metastases, and died within less than a year from the time of the original operation.

In order to estimate properly the value of operative treatment, we must first have a very clear and definite idea of the course of the disease when left to itself. Without going into details, or attempting to describe the various changes that may take place in cancer of the breast, which is treated of in another article in this volume, we may accept it as proven that spontaneous cure is unknown, and that the disease when not treated, always, sooner or later, ends in death. Various authors have estimated the duration of life in cancer of the breast, untreated, to be twenty-seven months, twenty-two months, twenty-six months, thirty-two months. The average duration of life in cases treated by the older methods of operation was thirty-nine months in two hundred and twenty-four cases collected by Gross. Of five hundred and nineteen cases, one-third was free from recurrence three years after operation, while of sixty-five not operated upon, only one was well after three years. The mortality of the older methods of operation was probably not far from one death in six, and the cures of cases collected by Gross were 9.5 per cent.

Accepting the theory that cancer begins as a local disease, the surgeon argues that there must be some period at which it can be removed without danger of return, although, as I have said, this period in some cases has already passed before the tumor has attained sufficient size to be recognizable by the patient. The results of the older (or the incomplete, as they are now called) methods of operation will now be compared with the modern or complete operations. In attempting to estimate the value of the old and the new methods, we must have some common standard of value, or some common understanding as to what is meant by the term "cured." For many years surgeons have accepted without reserve Volkmann's rule, which regards the three-year limit as the basis of cure. I believe that a more extended study of results would show us that the rule has too many exceptions to justify us in accepting it with the confidence which it at present enjoys. Recurrence may take place many years after an operation. In a paper on the latency or immunity after operation for cancer of the breast, read before the Medico-Chirurgical Society in 1889, forty-eight cases of late recurrence were collected by Shield. In twenty-nine, recurrence took place from nine to twenty-nine years after operation.

Billroth went so far as to say: "I think one may express himself more boldly [than Volkmann], and may declare that, if a careful examination by an experienced surgeon detects no return when one year has passed since the operation, one may be sure that there will be no local nor glandular recurrence, and may pronounce the patient as radically cured."

Later investigations, however, have proven Billroth's views to be erroneous, and the more we study the final results of operations for cancer, the more reason, I believe, shall we find for extending even the three-year limit of Volkmann.

The following cases observed by the writer are excellent examples of the long-continued latency of the disease.

F. V——, 72 years old; widow, no children. A twin sister had died of cancer of the left shoulder blade. Personal history: The tumor appeared in the left breast twenty years ago. It grew slowly in size and at the end of six months was removed by operation, the whole breast being excised. She remained perfectly well for seventeen years, when there was a local recurrence at the site of the scar. The tumor continued to grow slowly. An examination made three years after the recurrence was noted, showed a mass about four inches in diameter, situated in the region formerly occupied by the breast, and firmly attached to the chest wall. There was an area of ulceration

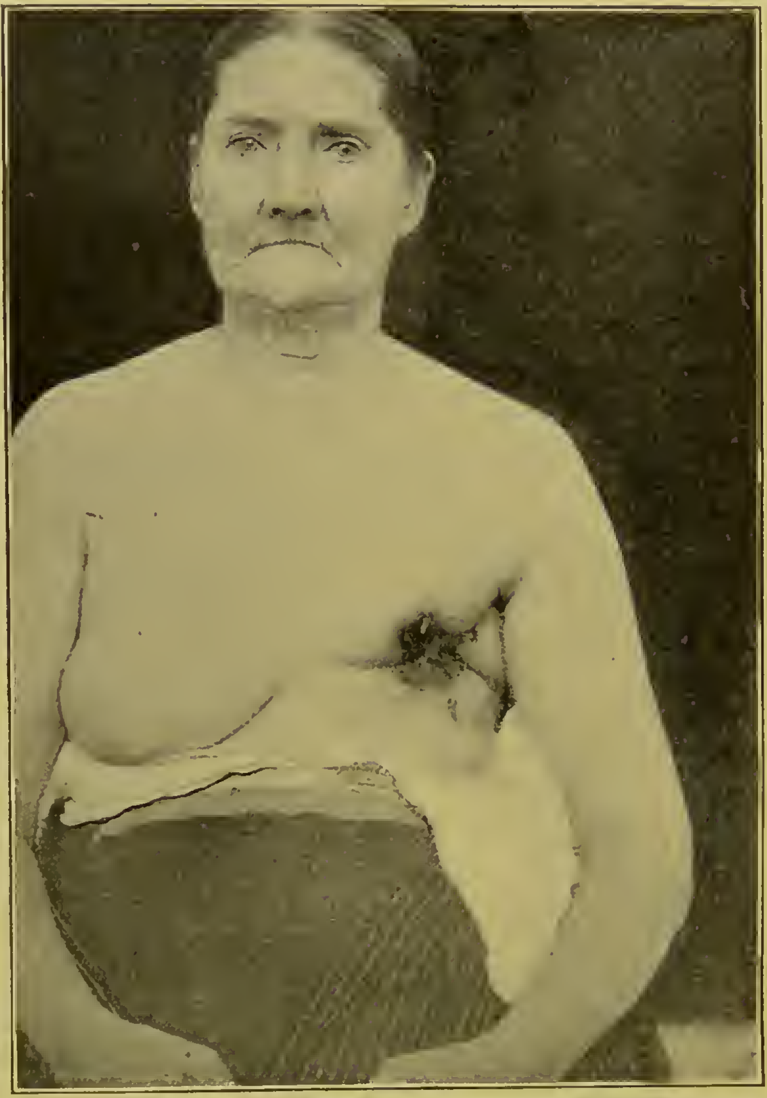

Fig. 5.—Carcinoma of the Breast. Local recurrence seventeen years after operation. (Original.)

the size of a silver half-dollar. There was no glandular involvement, either in the axilla or supraclavicular region, and no swelling of the arm.

Mrs. T——, aged 53, with good family history. She injured her left breast twenty-two years ago when nursing an infant. Ten years later a small lump was noticed in the same breast. The first operation was performed in 1885, the tumor being removed without excision of the breast. A second operation for local recurrence was performed in 1887. She then remained perfectly free from recurrence for seven years after the last operation, when a swelling was observed in the right axilla, close against the thoracic wall. The axillary tumor was removed by me October 2d, 1895. Microscopical examination showed it to be a typical carcinoma. It was found impossible to remove the entire disease. Shortly afterwards the arm became gradually swollen.

I have referred to the different lights in which recurrences are regarded by different writers. Billroth considered a case developing one year and a half after operation as having no connection with the original tumor, but looked upon it as an independent growth. However, few observers have gone so far as Billroth; yet there are many, and perhaps we might say the majority, who now regard cases developing three or five years after operation as independent tumors. This whole question must, I think, be studied in the light of new facts. I believe that a careful review of the subject of recurrent cancer will convince an unprejudiced observer that cancers developing long periods after removal of the primary growth are, in the vast majority of cases, true recurrences rather than developments *de novo,* and that they are due to the fact that at the time of the primary operation infected cancer cells were left behind, in either the glands or the region of the wound, or in many cases doubtless hidden in undeveloped metastatic deposits, where for a longer or shorter time they remained in a latent condition. That this explanation is neither impossible nor improbable is shown by our knowledge of tuberculous disease, which has so many points in common with malignant disease. To my mind it is another fact that seems to render more complete this analogy, and it adds another link to the chain of evidence that is being slowly forged in proof of the theory that cancer is also due to an infectious microorganism. It is not my province to discuss the etiology of cancer, and I simply call attention to the above as indirectly throwing light upon this question of late recurrences.

Halsted (*Annals of Surgery,* Vol. XX., 1894) states that of fifteen cases of late recurrences, in but one did the recurrence take place in the skin. He further adds that he has found no positive evidence of recurrence as late as three years, which was not in the scar in a broad sense of the word. From these facts he reasons very ingeniously that the probable explanation of many cases of local recurrence is that the tissues of the wound were, at the time of the operation, infected by the knife or instrument that had been in contact with cancerous tissues.

I believe this explanation may be true of at least a portion of recurrent growths, though it would probably apply with more force to those occurring soon after the operation than to those developing after a longer period.

Halsted has, however, emphasized what I believe to be a real danger, and one to which but few surgeons have called attention. It is a custom of many surgeons doing operations to cut through the tumor itself, in order to study its macroscopic appearance, and then, with the same instrument, without disinfecting it or the hands, to go on and complete the operation. This is a practice that should be strongly condemned. That the danger is a real one, and rests upon more than theoretical grounds, is shown by the fact that there are at present a number of cases on record in which an abdominal incision for malignant disease within the peritoneal cavity, especially when accompanied by ascites, has given rise to immediate and rapid development of malignant disease in the tissues of the abdominal wound, which were quite healthy prior to the operation. One such case has come under my own observation, being an extensive sarcoma of the ovaries, omentum, and mesentery, in a girl twenty years of age. Two weeks after an exploratory operation, there was a very marked infiltration of the abdominal wall at the site of the incision with sarcomatous tissue.

Frederick Dennis ("System of Surgery," Vol. IV.) cites a case in his own practice, in which infection presumably occurred from a knife that had been in contact with cancerous tissues, the disease recurring in a V-shaped incision which was made through healthy skin simply to relieve the tension of the flaps. Two other similar cases have been related to me by other surgeons.

I have personally seen rapid dissemination follow attempts to explore round-celled sarcoma, especially periosteal sarcoma of the femur, in a number of cases, and I am more and more convinced that such explorations, undertaken with either the knife or the tumor punch, are attended with no small risk in carcinoma as well as in sarcoma. In certain cases it is necessary for us to resort to such aids, but I believe the number of cases of this sort should be greatly restricted.

Metastases probably result from infected cancer cells entering the circulation through the thoracic and right lymphatic ducts. General dissemination rarely occurs before the lymphatic glands have become involved. Gross states that of 39 post-mortem examinations showing metastatic deposits of cancer, the glands were involved in 70.1 per cent.; hence in only 1 case out of 8 did dissemination occur without previous involvement or infection of the glands. As to the frequency of metastatic deposits, statistics vary. Gross states that in 374 cases metastases were presumed to be present in 83, or 22.19 per cent.; while of 78 cases in which post-mortem examination was made, they were found in 39, or 50 per cent. As to the time when they are most likely to occur, Gross states that out of every 100 cases 24 occurred during the first year, 21 between the first and second years, 27 between the second and third, and 28 after the third. While metastases may occur in almost any part of the body, they show a decided preference for certain localities. In 128 post-mortems collected by Gross, deposits were found in the axillary glands in 89 per cent.; in the liver in 42 per cent.; in glands other than axillary in 23 per cent.; in the pleura in 23 per cent.; in the lung in 20 per cent.; in the kidney in 3 per cent.; in the ovary in 5 per cent.

Results of Operation.—The accompanying table (p. 438), prepared with the assistance of Dr. E. E. Walker, by adding recent statistics to the very complete table of Watson Cheyne, shows in a condensed form the results of operations performed by the leading surgeons of the world.

In comparing the results of the complete operation with the incomplete, attention should be called to the fact that in some of the earlier statistics a very complete operation was performed. Volkmann excised the pectoralis major in some instances, the minor in thirty-eight cases. He did not, however, go so far as Halsted, inasmuch as he reserved this extensive operation for his worst cases, in which one or both muscles were involved, and he states that in only 11 of the 38 cases was there a recurrence in the scar. In 7 cases there was a glandular recurrence. In other words, in 58 per cent. there was either local or glandular recurrence. In the cases in which the pectoralis was not removed—the milder cases—there was a similar recurrence in 60 per cent., from which facts Halsted reasons that the excision of the pectoral muscles means altogether a more complete operation. In most of the discussions in which the advantages of the complete operation are set forth by its advocates, it seems to me that too great stress has been laid upon the importance of local or regional recurrence, and often the point of chief importance, viz., the final cure of the patient, has been lost sight of. It matters little, so far as the welfare of the patient is concerned, whether he dies as the result of metastases or of local recurrence. It would appear that the only fair way of estimating the value of any method of operation for cancer of the breast should be based on the final results as regards the cure of the patient. If the disease is already so far advanced at the time of the operation that the pectoral muscle or its fascia has become infiltrated with carcinomatous cells, the probabilities are very great that metastases have already occurred, or that the supraclavicular or mediastinal glands have become hopelessly in volved.

STATISTICS OF BREAST OPERATIONS.

Operator.	Total cases.	Mortality Per cent.	External recurrences, local and glandular. Per cent.	Total known recurrences or deaths from metastases. Per cent.	Percentage of Cures.	CASES OPERATED UPON MORE THAN THREE YEARS BEFORE THE REPORT.			Cases well beyond three years after operation.
						Total.	Recurrences (or metastatic deposits). Per cent.	Cures. Per cent.	
Fischer (Henry)	147	20	....	55	8	86	59	15	13
Esmarch (Oldekop)	229	10	....	44	10	171	(?)	14	25
Before 1863	...	....	....	....	....	47	....	4	2
After 1863	...	....	....	....	....	124	....	18	23
Rosc (Fischer)	61	26.3	....	(?)	6	....	....	....	4
Billroth (Winiwarter)	143	23.7	....	62	5	89	68	9	8
Trendelenburg (Neuendorff)	97	11	....	54	2	50	68	4	2
Lücke (Dietrich)	110	7.6	....	(?)	9	69	60	13	9
Czerny (Schmidt)	150	4.4	....	(?)	5	82	46	8.5	8
Krönlein (Horner)	144	4	....	58	18	121	68	20	25
Küster (Schmidt)	222	10.8	....	(?)	9	132	(?)	15	20
König (Hildebrand)	135	....	....	....	17	118	61	20	23
Bergmann (Eichel)	114	4.3	....	62	11	43	62	30	13
Mitchell Banks	82	12	....	26.8	21.9	....	....	....	18
Halsted (recent report)	133	(?)	26.3	....	30	76	....	41	31
Watson Cheyne	61	1.6	18	32	19.9	21	42.8	57	12
Volkmann	131	7	47	61	11.4	125	....	12	15
Billroth up to 1877	305	15.7							
1877 to 1879	68	....	....	....	5.8	....	....	....	4
Middlesex Hospital	98	12.2	48.9	....	8	....	....	....	8
Reports, 1885	19	5.2							
Smith, Sir Thomas (T. Rudolph Smith)	41	....	68.2	82.9	....	....	....	42.6	17
Warren, J. C	72	2.7	47	69.4	23	55	23	30.9	17
Gross, S. W	43	3.7	30.55	....	18	38	....	21.05	8
Dennis	74	1.3	....	....	23	38	5	45	17
Dowd	29	0	....	....	....	6	3	50	3
Bull	118	3.4	....	....	17.2	75	....	26.7	20
Weir	125	0	....	....	....	60	....	20	16
Helfcrich	92	....	36	51	25	....	....	....	24
Prior to 1890	57	....	40	57.9	24.5	....	....	....	14
Since 1890	35	....	28.5	40	28.6	....	....	....	10
Total	3,135	....	....	....	....	....	....	....	409

The statistics of Helferich (*Deutsche Zeitschrift für Chirurgie*, Bd. 44) which contain some of the most useful data that we possess with regard to the value of operative interference in cancer of the breast, show that in not a single case in which the pectoral muscles were involved at the time of operation did final cure ensue. If, therefore, it is true, as statistics would seem to show, that the disease is practically incurable when the pectoral muscles have become involved, the question naturally arises: Why subject the patient to the extensive operation of removal of the muscles when they are *not* involved? One reason for this extensive operation, emphasized by Halsted and others, is that removal of the pectoralis alone permits of perfect removal of the contents of the axilla. We must admit that it certainly does greatly facilitate the dissection of the axillary glands, yet in the majority of cases I believe the dissection can be done without interfering with the pectoralis. The removal of these muscles cannot fairly be cited as the cause of the very great improvement in the matter of external recurrences in Halsted's statistics. His external recurrences, local and regional combined, amounted to 22 per cent. in his earlier statistics of the complete operations, and 26.3 per cent. in his latest statistics, an enormous improvement over the results of the incomplete operations, in which there were about 75 per cent. local recurrences. Yet Watson Cheyne ("Objects and Limits of Operation for Cancer," 1896, p. 33), who does not believe in removing the pectoralis except in rare cases, had only eighteen per cent. of local recurrences, a considerably lower percentage than Halsted. These statistics of Cheyne's would seem to show that the dictum of Halsted, that the pectoralis should be removed in every case, cannot be considered as definitely proven. I agree with Cheyne, who states that removal of the pectoral muscles is not necessary unless there are actual nodules in the substance of the muscle.

In the manner of operation described by Cheyne there is no difficulty whatever in pulling up the remains of the pectoral muscle sufficiently to obtain complete access to the upper part of the axilla. Cheyne further states: "Where the glands in the axilla are markedly enlarged, the question arises as to how far one should go. In the first place, under such circumstances it is certainly well to see what one is doing. While if the pectoral muscle is not affected at all, I prefer leaving it; I think it is well to divide it transversely, and after the operation to stitch it up."

Another and very important question which cannot be regarded as settled, is the treatment of the posterior triangle of the neck. Halsted believes that this triangle should be opened up in every case and the supraclavicular glands should be removed, whether enlarged or not. In nearly every authority on the operative treatment of cancer, it is laid down as a cardinal rule that the palpable enlargement of the supraclavicular glands constitutes a contraindication to operative interference. We must admit that the supraclavicular glands in many cases are affected with carcinomatous cells before they are palpably enlarged. Whether the removal of these glands at this stage of the disease will cure the patient, is the question before us, and one which we cannot settle without many more facts than are at present at our disposal. No one, as far as I know, with the exception of Halsted, has reported a case of final and complete cure of cancer after the disease had extended to the supraclavicular glands.

Cheyne states that, "if the highest axillary glands are notably involved, it stands to reason that the posterior triangle of the neck should be opened. Unfortunately, however, in these cases the line of infection does not so much run up in the line of the posterior triangle, as along the subclavian vein into the thorax, along a route which is only imperfectly accessible, even if the posterior triangle is opened, and I have not seen much benefit in the way of finding or rooting out the disease as the result of opening up this triangle. Mr. Arbuthnot Lane advocates division of the clavicle and clearing out the supraclavicular glands in many cases, but this is a method which I cannot at all agree with, and I think that my results bear me out. Where the disease is noticeable in the supraclavicular glands, I believe their cure is hopeless."

The following is Halsted's operation, as described in the *Annals of Surgery*, 1894 and 1898. First, the skin incision is carried at once everywhere through the fat. The triangular flap of skin, containing nothing but skin, is reflected back well towards the posterior axillary line. The fat which lines the flap is dissected back to the lower edge of the pectoralis major muscle, where it is continuous with the fat of the axilla. The costal insertions of the pectoralis major are severed and the splitting of the axilla, usually between its clavicular and costal portions, is begun and continued to a point about opposite the scalenus tubercle on the clavicle. The clavicular portion of the pectoralis major muscle and the skin overlying it are cut through close to the clavicle. This exposes the apex of the axilla. The loose tissue under the clavicular portion (the portion usually left behind) on the pectoralis major is carefully dissected from this muscle, as the latter is drawn upwards. The splitting of the muscle is then continued to the humerus, and the part of the muscle to be removed is cut close to its humeral attachment. The whole mass of skin, breast, alveolar tissue, and fat, circumscribed by the original skin incision, is raised up with some force, to put the submaxillary fascia on a stretch as it is stripped from the thorax, close to the ribs and pectoralis minor muscle. It is well to include the delicate sheath of the minor muscle when this is practicable. The lower and outer border of the minor muscle having been passed and clearly exposed, this muscle is divided at right angles with its fibres, at a point a little below its middle. The tissue over the minor muscle near its coracoid insertion, more or less rich in lymphatics and often cancerous, is divided as far out as possible, and then reflected inwards in order to liberate or prepare for the reflection upwards of this part of the minor muscle. The subclavian vein is exposed at the highest possible subclavicular point. The contents of the axilla are dissected away with much care. The glands should not be pulled out with the fingers, but dissected with a sharp knife. It is advised to remove all of the loose tissue above the vessels about the axillary plexus of nerves. The vessels having been freed, the axillary contents are then stripped from the inner wall of the axilla, the mass to be removed being held firmly by the left hand, putting on a stretch the delicate sheath which combines it to the chest. This fascia is cut away close to the ribs and to the serratus magnus muscle. The subscapular vessels become nicely exposed, and are caught before they are divided. The subscapular nerves may or may not be removed. Küster strongly urges leaving them, while Halsted states that the importance of so doing is not yet entirely settled. The entire mass, including tumor, subcutaneous and axillary fat, is removed in one piece.

In a very recent paper giving the results of operations for cancer of the breast performed at the Johns Hopkins Hospital from 1889 to 1898 (Transactions of the American Surgical Association, 1898), Halsted states that his present method of operating is even more radical than that employed at the time of the first publication. He states that the supraclavicular region is almost invariably cleaned out. He no longer divides the clavicle as he did five or six years ago, believing that its simple division does not much facilitate dissection. He says that, if it were very desirable to remove the supraclavicular contents in one piece with the axillary contents and breast, one need not hesitate to excise, if necessary, even the entire clavicle. But the removal of the supraclavicular fat and lymphatics is best done from within outwards and from below upwards, the subclavian vein being the starting-point of both infra- and supraclavicular regions. To excise the supraclavicular tissues, he uses the vertical incision, parallel with the sternomastoid muscle, near its posterior border. The few posterior fibres of this muscle are divided, and the junction of the internal jugular and subclavian vein is exposed. The dissection is begun at the angle or junction of these veins. The omohyoid muscle is divided in its tendinous portion.

The supraclavicular fossa has been cleaned out in 67 cases at the Johns Hopkins Hospital. Cancer was found in the tissues removed

23 times, or in 34 per cent. of these cases. In 30 cases there was no cancer and in 14 the tissues had not at the time of the report been exhaustively examined. Of the 67 operations 53 were primary operations, having been performed at the time of the removal of the breast, while 14 were performed subsequent to the original operation, and because the supraclavicular glands could be palpated. The results of this very large number of operations are exceedingly interesting and important. Halsted states that in four cases the patients were alive and apparently free from metastases three or more years after the primary operation, although in these cases the operation upon the neck was performed secondarily. Two of these patients were living and well at the time of the report, more than four years after the primary operation, and three and three and a half years after the operation upon the neck. In one of these cases a portion of the clavicle was dissected.

Of the fifty-three primary neck operations, the supraclavicular glands were found involved in twelve cases, or twenty-three per cent. Unfortunately, nothing is said of the subsequent history of these cases. Therefore, the only positive evidence Halsted's statistics afford us as to the value of this operation of cleaning out the supraclavicular fossa rests upon two cases in which the operation was done secondarily, and in which the patients remained well three and three and a half years after the operation. In view of what I have already said regarding the failure of three-year limit as establishing a cure of the disease, we cannot consider the question as settled without much stronger evidence. Halsted argues that the neck involvement is no more serious than that of the axilla. The neck can be cleaned out just as thoroughly as the axilla. He believes that we shall in the near future remove the mediastinal contents at some of our primary operations. After reviewing the cases in which the operation upon the neck has been performed, he concludes that "it would appear that for the present our rule should be, *operate on the neck in every case.* The neck operation should not be postponed for a second act." In the main operation he states that some changes have been made. He now removes the clavicular as well as the major pectoral muscle, dividing the insertion of the major and then its origin, and the origin of the minor before exposing the subclavian vein. This vein is first exposed at its inner part, and the axilla is stripped of its contents and its anterior wall at one time, from within outwards and from above downwards, as before. The skin incision remains the same as in the original operation. He still further emphasizes the dangers of exploratory incisions, having been deeply impressed with the large number of cases in which general dissemination of the malignant growth apparently followed quickly upon exploratory incisions. He states that breast tumors should not be incised on the operating-table prior to their removal. The surgeon must learn to recognize malignant tumors, not only with the microscope, but also with his naked eye and fingers.

Shield, in his recent work, has drawn a very interesting comparison of the results of Sir Thomas Smith (published in the *Lancet*, August 18th, 1896), and those of Halsted, and one very important point brought out by these statistics is that to which I have already referred, namely, that the high percentage of local recurrences is not always inconsistent with comparatively good final results. Of 35 cases of Sir Thomas Smith's, local recurrence followed in 26, or 74 per cent. Taking the usual three-year limit as the basis of cure, 15 cases remained well beyond three years, or giving a proportion of 42.6 per cent. of "cures." As Shield points out, the percentage of local recurrence is certainly high, and some of the patients who lived the longest had the largest number of local recurrences. Some of the patients were alive thirteen and seventeen years after operation. Comparing this with Halsted's 50 cases, reported in the *Annals of Surgery* in 1894, there are only 6 per cent. of so-called local recurrences; but including the regional, as should fairly be done, the percentage of local recurrence is 22, 10 patients died of metastatic deposits and 11 others were not traced. But 2 women were well over three years. Since the publication of Shield's work, Halsted has published a paper giving his results up to April, 1898; and, inasmuch as he has now been able to trace 76 of 133 cases beyond three years, we have a much fairer basis for comparing the operation with Sir Thomas Smith's than the earlier statistics used by Shield.

Of the 76 patients operated on over three years ago, 41 per cent. were alive and well without local recurrence and with no sign of metastases, 10 died more than three years after operation, but 1 of them having local recurrence, the other 9 dying of metastases. Halsted states that some of the 10 patients who died after three years may have had at three years signs of metastasis, though he is unable to make a positive statement as to his point. Thirty-five, or 46 per cent., died within three years of the operation, and 7 had local recurrence. Of the total number of cases operated upon (133), 35, or 26.3 per cent., had local or regional recurrence.

Sir Thomas Smith's cases furnish us with new and very important data in proof of what I have said regarding three years as establishing a cure. While 15 cases out of 35 remained well for three years and over, giving a proportion of 42.6 per cent. of "cures," 9 cases recurred after the three-year limit had passed, thereby lowering the proportion of actual "cures" from 42.6 per cent. to 17.1 per cent., a very notable difference.

The statistics of Watson Cheyne should be pointed out as showing the best results yet obtained by operative treatment of cancer of the breast, the proportion of local recurrences having been but 18 per cent. Twelve out of 21 cases traced beyond three years were free from any evidence of local or general return, giving 57 per cent. of estimated "cures."

Bennett May, in his Ingleby Lectures (*British Medical Journal*, May 29th, 1897), discusses Halsted's operation as follows: "I think it is very doubtful whether some of these modern extensive operative procedures confer any additional immunity from recurrence at all commensurate with their severity. It is clear that in both classes of operation the majority of fatal cases die of internal metastases without external recurrence; and against internal metastases no operation can protect. It is very certain that but little good can result from these extensive measures, if there exists some deep-seated nidus of infection which is beyond the reach of the knife."

Rudolf Matas, of New Orleans, in a discussion upon the operative treatment of cancer of the breast, at a meeting of the American Surgical Association, April, 1898, in reply to the question "Can we expect still better results from more extensive and aggressive operation, or must we now depend solely upon earlier diagnosis to increase the effectiveness of present procedures?" states:

"So far as I am concerned, and judging purely from my personal experience with Halsted's and Meyer's operations, I firmly believe that surgery has here nearly reached, if it has not already attained it, maximum expression of effectiveness, beyond which it is absolutely impossible to advance without great risk to life or with any further expectation of increasing the chances of permanent recovery. It is clearly fixed in my mind that all surgery can do is to thoroughly eradicate the primary focus of infection in the breast together with the most frequented extrathoracic routes of lymphatic contamination; beyond this it is impossible to go with any reasonable prospect of success."

Matas has had considerable experience with Halsted's operation, and a comparison of the results with the results of his earlier and less complete operation is of interest. Since 1894 he has operated upon a series of cases, 15 in number, by the complete methods of Halsted and Meyer. Two patients died of accidental causes not connected with the operation. Of the remainder 5 were living (none beyond three years) and 8 died. In 5 cases there was local recurrence (33.3 per cent.). In 3 cases death was due to metastases.

Comparing these results with those of 12 cases operated upon prior to 1894 by the earlier methods, 5 remained well beyond three years, or 41 per cent. Including 1 patient that recovered after three recurrences, his recoveries or estimated cures reach 60 per cent. These results of incomplete operation (only 33 per cent. of total failures) are in striking contrast with the 67.7 per cent. of total failure following his series of cases operated upon by Halsted's method. Matas from his personal experience concludes that "in advanced cases in which the upper axillary, subscapular, and posterior cervical lymphatics are markedly involved, Halsted's operation offers no more prospect of cure or chance of escape from internal metastases and secondary recurrence in the neck than the older and less mutilating operations. The new operation will unquestionably greatly diminish the probability of *local recurrence*, but the patient will die, as a rule, just as quickly from regional and internal metastases as if a superficial operation had been performed."

It is but fair to state that Matas, in spite of his own discouraging results, is still a firm believer in Halsted's operation. These results, to my mind, show the impossibility in such a subject of drawing correct conclusions from any small series of cases. They still further prove that the question is a most complex one and at present impossible of solution. No matter what our attitude may be in reference to the advisability of adopting the method of Halsted as a routine measure, no one can fail to appreciate the enormous value of Halsted's work. Whatever be the final solution of the question, that solution will be due in no small measure to the elaborate and painstaking investigations of himself and his associates.

I believe that the true explanation of the statistics of Matas and Smith and of the apparent inconsistency of comparatively good final results occurring with a high percentage of local recurrence is as follows. In the majority of cases that result in final cure after any method of operation the disease has probably not extended at the time of operation far enough beyond the original tumor to cause a local or general recurrence. For the sake of a concrete example, suppose we place the number at twenty per cent. of the cases operated upon, the other eighty per cent., if operated upon by the complete method of Halsted, would show, *e.g.*, twenty-five per cent. of external recurrences, and if by the incomplete, eighty to one hundred per cent.

This does not necessarily mean that the number of final cures will be increased by anything like this proportion after the complete operation, but that the disease which has extended in various directions and through various channels has not only involved the outlying tissues of the breast and the axillary glands which are removable by the complete operation, but that it has also involved other regions not accessible to the surgeon, as, for example, the mediastinal glands, or the bone marrow; hence, although the surgeon may be able to prevent a local or external recurrence, he cannot prevent the development of metastases from the hidden source of infection just described.

This explanation is not offered as a plea in favor of going back to the older methods, but simply as a way to harmonizing facts which seem to be at variance. No one can study the pessimistic teachings of a quarter of a century ago as regards the curability of cancer of the breast without feeling that a great step in advance has been made by our modern methods. The mortality of operation has been lowered from sixteen per cent. to less than two per cent., and the estimated cures have risen from nine per cent. to probably about twenty-five per cent. These facts, encouraging as they are, should not, however, lead us so far in the direction of extensive operation as to make us forget that, after all, surgery of malignant disease of the breast is but a part of general surgery of malignant disease, and should be performed according to the general surgical and anatomical principles that hold good for other parts of the body, and for malignant disease in general.

Shield, after very carefully and judiciously reviewing the results of the old and new methods, concludes: "From what has been said it is clear that much difference of opinion still exists, and I feel confident that we need more extended and prolonged observation in cases submitted to such operations as those of Halsted and Meyer before we can universally adopt them. The swing of the pendulum of surgical opinion is generally extreme, and has now turned from too slight to too extensive operating."

Indications and Contraindications for Operation.

Operation should be strongly urged in all cases of cancer, including sarcoma of the breast, in which there is a reasonable prospect of the surgeon being able to remove the entire disease. If the skin is involved, a very wide area of skin should be removed without any regard to subsequent closure of the wound. The pectoral fascia and the axillary glands and fat should be removed in every case. If there is any evidence of infiltration of the pectoral muscle itself, the muscle should be removed, although in such cases, as the statistics of Helferich prove, the prospect of cure is very slight. If the glands in the axilla are extensively involved, it may be wise to remove the pectoralis major muscle in order to facilitate the dissection of the axilla, even though the disease does not involve the muscle itself.

As regards the prognosis, it may be said in a general way that the more chronic the type of cancer the greater the probability of a cure, and even if recurrence takes place, it is likely to be long delayed. In cancers of very rapid growth, in which the skin is early and extensively involved, the prognosis is almost absolutely bad, no matter what form of operation be employed or how soon it be performed. Taking the cases as they occur, without selection, operated upon along the lines laid down, there is a reasonable prospect of freedom from a return of the disease for at least three years in one-third of the cases. The mortality from the operation, in the hands of skilled surgeons, is at the present day about two per cent. The more extensive operation advocated by some—that of resection of the clavicle and amputation of the shoulder-joint, for carcinoma of the breast—I believe to be rarely if ever justifiable. Of such operations Shield well says: "They are severe in performance, painful in endurance, slow in healing, and almost inevitably disappointing in the ultimate result." Operations performed in cases in which the surgeon is sure that the disease cannot be completely removed not infrequently cause rapid increase in the growth of the lesion.

PALLIATIVE TREATMENT.

Williams states that it is desirable for cancer patients to live in a dry, warm climate, where there is plenty of sunshine. I believe this advice to be exceedingly good. An experience of several years as surgeon in charge of the Incurable Ward of the New York Cancer Hospital has thoroughly convinced me of the unmistakable influence of the weather on patients suffering from cancer. On clear, bright days, when the air was free from humidity, the pain and discomfort of the patients were reduced to a minimum; while, on the other hand, during cold damp weather, the change was very striking. We were forced to give larger doses of sedatives. The pain and discomfort of the patients were very greatly increased.

Many writers advise against a meat diet. Williams strongly recommends the use of bromide of potassium, and frequently employs it in combination with Fowler's solution. Hot applications are as a rule contraindicated, as they increase the discomfort and burning. If areas of ulceration are present, I have found the greatest relief to come from the use of powdered orthoform, either alone or in combination with bismuth subgallate, or nosophen, in the proportion of two to one. It may also be used as an ointment, though the anæsthetic effect is less marked than when used in the powdered form. The anæsthetic effect from the use of orthoform is very similar to that of cocaine, except that it is continued for nearly twenty-four hours. If there is much sloughing, dressings of permanganate of potassium, or sanitas, or camphophénique, will be found of service.

Cancer of the Rectum.

Carcinoma of the rectum is an affection of middle and advanced life, rarely making its appearance before the thirty-fifth year. According to statistical data, it appears that men are more subject to the disease than women, in the proportion of six to five. The most frequent form of the disease is that taking its origin from the so-called crypts or follicles of Lieberkühn, located above the sphincters. If the affection be epitheliomatous in nature, *i.e.*, originates at the muco-cutaneous junction, we have to deal with a condition which, in appearance and involvement of neighboring tissues, resembles epithelioma of the lip; the changes in the symptoms being referable only to the alteration in the function of the parts involved. The other forms of the disease, as the colloid and scirrhous types, do not call for separate consideration in this place, as the essential difference lies in the rapidity of development and course. As to frequency, it may be stated that about four per cent. of all carcinomata occurring in the human subject are confined to the rectum; hence the importance of an early diagnosis cannot be overestimated. But nowhere in the body are so many elements combined to render a diagnosis difficult, the symptoms depending entirely upon the primary location and type of the disease.

SYMPTOMS.

The attention of the patient may be first directed to the condition by an uncomfortable feeling of weight and heaviness in the pelvis, accompanied by an indefinable sensation of annoyance during and after defecation. As the disease progresses, these ill-defined symptoms assume a more definite character, the feeling of heaviness becomes one of distention, and the sensation of annoyance, as a rule, gives place to one of pain. The stools are scanty and more frequent, and instead of well-formed movements, porridge-like masses, covered with slime, are evacuated. Constipation alternates with diarrhœa. Later on, the calls to stool become more urgent, the dejecta being composed chiefly of mucus, pus, and a few scybala, perhaps streaked with blood. A dozen or more times a day ineffectual efforts to empty the bowels are made, temporary relief only being obtained by the passage of muco-purulent matter, the sensation of fulness, however, remaining. If the growth is located at the anal margin, control of the sphincters is lost early in the disease. If the disease is located above the sphincters, the loss of sphincter-control comes on later and then appears to depend upon nerve involvement.

The nature of the pain generally depends upon the position of the growth. If the sphincters are involved, the pain is most intense, lancinating in character, radiating from the rectum through the perineum and down the thighs and legs. If the affection is seated in the upper part of the rectum or lower portion of the sigmoid, the pain is less intense, and severe only after irritation due to the passage of the bowel contents.

As the cylindrical-celled, or glandular type, of carcinoma of the rectum starts by invasion of the submucosa, the early stages of its development are unattended by an appreciable discharge. Only with penetration of the mucosa as a tumor, and growth into the lumen of the bowel, does ulceration of the neoplasm occur, followed by a discharge composed of pathologically altered secretion from neighboring glands, detritus from the ulcer surface, and blood from eroded vessels.

Diarrhœa, so constantly present in this affection, is caused by the chronic obstruction which exists from the time the constriction at the seat of the disease encroaches upon the lumen of the gut, allowing only the fluid and soft fecal matter to pass. The retained solid portions of the fæces irritate the intestinal mucosa, giving rise to violent peristalsis and copious secretion from the intestinal glands. This secretion softens the scybalous masses, which are then evacuated in part. Distention of the bowel and atrophy of the intestinal glands follow frequent repetition of this process, until complete obstruction supervenes.

Emaciation and the characteristic cancer cachexia may make their appearance early in the disease. The disease steadily advances, involving the contiguous organs. The bladder, prostate, and urethra may be involved in the male; and the vagina, uterus, tubes, and ovaries in the female. As the ulcerative process extends deeper into the tissues, false passages may be established into the male bladder and into the vagina in the female; while the fæces are discharged through these routes as well as by the natural opening. Metastases may occur at any period, the liver being a favorite seat. Death usually occurs from exhaustion, obstruction, metastastic deposits, or general cachexia.

DIAGNOSIS.

Physical examination, and a few indefinite local symptoms referable to almost any disease of the rectum, are the only means of establishing a diagnosis early in the disease. Hence a rectal examination in all middle-aged individuals complaining of rectal symptoms is absolutely necessary.

The growth may be seen at the margin of the anus; it may be felt by introduction of the finger; or it may be necessary to use a long speculum to reveal the area between the promontory of the sacrum and the iliac fossa. If the growth is at the margin of the anus, a hard, indurated mass with everted edges, possibly ulcerated, protrudes above the surrounding surface; the anus is thickened and fissured here and there from loss of its elasticity. The extent of induration and the degree of constriction of the parts are in direct ratio to the duration of the disease. This condition may be confounded with a chancroidal or tuberculous (lupoid) affection; but the history, the presence of cartilaginous induration, and the ease with which a specimen for microscopical examination can be obtained, will generally lead to a correct diagnosis.

If the growth is located in the rectum, but within reach of the finger, and ulceration has not yet occurred, great delicacy of touch and a large experience are necessary to determine the nature of the affection. Even at a later period, when ulceration is well defined and easily detected, recognition of the malignant or non-malignant nature of the process is not always a simple matter. The treatment depends upon the diagnosis, and at this stage a carcinoma of the rectum may be cured.

Instruments are of value only in so far as they facilitate detection of the extent and location of the disease; and these cannot be as readily made out as by the aid of the finger, which, if properly trained, is the only true guide.

Carcinomatous ulceration presents to the touch a well-marked area of induration with hard and very irregular margins. The induration extends diffusely beyond the edges of the ulcer, gradually fading into the surrounding tissues. In other forms of ulceration, simple syphilitic, dysenteric, and traumatic, the contour is regular, the induration comparatively slight, and the edges of the ulcer are soft and flexible. If the ulceration has existed for a number of years and been subjected to the action of escharotics, etc., the character of these types will be altered; the chronic history will, however, aid in differentiation. Should the carcinoma be grafted upon an old, non-malignant ulceration, the further progress of the affection will determine its nature.

In that stage of the affection in which the growth involves the whole circumference of the bowel and encroaches upon the lumen and surrounding tissues, the examining finger distinctly maps out the difference between the healthy and the diseased rectal wall. It recognizes the stricture, and by careful palpation the degree of mobility of the canal is determined. This feature should not be overlooked, as it permits recognition of any involvement of surrounding organs. Should the stricture be too narrow to readily allow introduction of the finger, force should never be employed in an effort to get beyond the constricted portion of the gut, as the diseased tissues are very friable and rupture of the bowel may easily occur. Such an accident would very probably result in peritonitis and death. The rapidity of the course of this disease renders diagnosis at this stage of the affection comparatively simple. Non-malignant strictures usually give a history of years of suffering; furthermore, they are unattended by involvement of surrounding structures and the general symptoms of cancer. In consistence these structures are softer to the touch, and their surfaces more regular and not corrugated and furrowed; they are ulcerated in one spot and non-ulcerated in another, as in carcinoma.

When the disease is too low in the pelvis to be palpated through the abdominal wall, and too high to be reached by the finger per rectum, instruments are to be resorted to. The various specula, tubes, and bougies devised for rectal inspection and exploration, *i.e.*, the sigmoidoscope and the colonoscope, etc., are too well known to require more than the statement that their length varies from three to eighteen inches. The Kelly tubes, or modifications of them by Kelsey and Martin, are the best instruments for obtaining a view of the diseased area. They can be introduced into the rectum and through the sigmoid into the colon. The mucous membrane of the bowel and any changes in its surface can readily be seen by reflected light. In addition to the sigmoidoscope, bougies are of value to determine the degree of stricture when less than three-quarters of an inch. They determine the extent of the disease by touch only. Small mirrors, resembling those of the laryngoscopist, may be employed to determine the condition of the bowel above any stricture that may be impassable for the tube. Any portion of the diseased area which is held up by the cicatrices of the old ulceration and does not readily fall over the end of the instrument, can easily be observed and studied by their aid. As is the case in laryngoscopy, special training is necessary to interpret what is seen. The untrained will find a stricture where none exists. Prolapse of the mucosa over the end of the speculum effectually blocks the way unless avoided by manipulation of the instrument. Sometimes the injection of fluid to distend the bowel in front of the instrument is required. The promontory of the sacrum is always in the way of the colonoscope, and here force and a lack of knowledge of the anatomy of the parts may do great damage. In the hands of a skilful operator this instrument can be passed without force, and no violence should at any time be exerted.

TREATMENT.

There is no *palliative* systemic treatment of cancer of the rectum worthy of the name. The general condition calls for opium to relieve pain, laxatives to prevent obstruction, and enemata to avoid accumulation of secretions and consequent septic absorption. The diarrhœa, a more frequent complication than obstruction, is sometimes very difficult to control. Rest, easily assimilated food, as a meat and milk diet, and bismuth and morphine are the most effective means.

Palliative *local* measures will generally do more harm than good, as any source of irritation to the growth hastens its advance. Occasionally, when the patient refuses operation, slight help may be given by dilating the stricture or by curetting away part of the sloughing growth.

Operative Treatment.—When the general health suffers from the chronic obstruction and constant pain and tenesmus, colostomy and excision of the rectum are the only measures capable of giving any prolonged relief.

Colostomy.

Colostomy relieves the obstruction and lessens pain and tenesmus, for the irritation produced by passage of the fæces over the ulcerated surface ceases. The rectum being no longer used, nature allows it less blood supply; the congestion attendant upon its activity gradually subsides and the growth of the carcinoma is in so far retarded. The objections to the operation are that the fæces are passed in an unnatural position and that diarrhœa occasions discomfort, not only to the patient but to those who are associated with him, as in this position it is extremely difficult to control fluid material. Notwithstanding these objections, the operation gives decided relief and prolongs life for from one to five years. Death following colostomy is usually due to exhaustion or metastases, and the patient escapes the tortures attendant upon intestinal obstruction. This operation is indicated only when the rectum and surrounding tissues are so involved that any radical operation would be followed by death from shock or by almost immediate recurrence in the wound. The risks attending a colostomy are very slight and should not involve loss of life.

A colostomy may be performed anywhere in the colon, the main object being to get well above the disease. The favorite sites, however, are the left lumbar and inguinal regions. The lumbar operation, Amussat's, was at one time very much in favor. It was advocated because the peritoneum was not opened. This artificial anus was, however, awkwardly placed and difficult for the patient to keep clean. The field of operation was limited and great difficulty was found in locating the colon if it had a mesentery. At the present day, when the peritoneum is opened without fear, this operation is of value only in cases of great distention from obstruction, or when the disease is situated high up in the sigmoid flexure beyond the point where the usual inguinal opening is made.

Lumbar Operation.—Beginning at the left of the vertebral column, the incision should be made along the crest of the ilium, extend downwards and forwards for four or five inches and parallel with the crest of the ilium. The skin, muscles, and fascia of the abdominal wall are divided down to the outer edge of the quadratus lumborum and transversalis fascia. These are next divided, and the colon having been found, it is drawn into the wound opening. A glass rod, silver-wire suture, or other material may be used to draw the posterior wall as close up to the surface as possible, the object being to make a firm spur to prevent the passage of fæces beyond the artificial anus into the rectum. The bowel should be attached to the edges of the incision by a number of silk sutures passed through the skin and muscles, then through one of the longitudinal muscular bands in the wall of the colon. The reason for including one of the longitudinal muscular bands is to avoid the danger of the sutures tearing out; this accident may also be overcome by employing a large number of sutures. The sutures should not pass through the lumen of the bowel, but through the serous and muscular coats only. The bowel may then be incised, or, as some surgeons prefer, left for forty-eight hours unopened, if there are no urgent contraindications.

Inguinal Operation.—This operation should be preferred to the lumbar for the following reasons: (*a*) Under the present aseptic peritoneal toilet the danger is no greater than in the lumbar operation; (*b*) the whole of the abdominal cavity can be explored, and the extent of the disease and any involvement of sacral, pelvic, or mesenteric glands detected; (*c*) the anus is in a convenient position, and can be seen and attended to by the patient; (*d*) the distal end of the bowel can be kept clean by irrigation self-administered; (*e*) the artificial anus can more readily be closed than in the lumbar operation; all of which advantages are not offered by any other operative procedure.

The incision used by Kelsey of New York and Cripps of London is perfectly satisfactory. An imaginary line is drawn from the anterior superior spine of the ilium to the umbilicus. An incision is made three inches in length, across this at a distance of one inch from the spine. The abdominal muscles are divided down to the peritoneum, which is picked up with thumb forceps and incised. The edges are caught with clamps at intervals of a quarter of an inch all around the opening. The colon may bulge into the wound or it may be masked by coils of small intestine; if the latter is the case, the finger should be passed well down into the pelvis until the promontory of the sacrum is felt. The coil of the bowel is hooked up by the finger and gently drawn into the incision. If the colon is the portion of the intestine grasped, which can be recognized by the appendices epiploicæ and the longitudinal bands, the nearest point above the disease and that which comes easily into the incision is selected for the formation of the anus. This part should be brought out on to the abdominal wall and surrounded by hot towels. A silver-wire suture is then passed, about one inch from the centre of the incision, through skin, muscles, and peritoneum, through the mesentery of the bowel and out on the other side of the incision, and then drawn tight and shotted. Care should be taken to avoid including in the clasp of this suture any other portion of the bowel. This brings the posterior wall of the colon well up to the surface of the abdominal wall, making a spur which prevents the passage of fæces beyond the artificial anus into the diseased and distal end of the bowel. The excess of the bowel being returned to the abdominal cavity, a row of silk sutures is passed through the skin, peritoneum, and longitudinal bands in the gut, as in the lumbar operation. Twenty sutures, eight on a side and two at each end, are generally sufficient to give close apposition. The protruding portion of the bowel is then cut level with the abdominal wall. Irrigation with hot saline solution is employed to wash away escaping bowel contents. The author, after opening the colon, over-stitches all the coats of the cut edge of the bowel completely around its circumference. This immediately arrests all oozing, and, to a great extent, prevents prolapse of the mucous membrane, which is sometimes an annoying complication at a later period. The large number of sutures used lessens the danger of the escape of intestines and the chances of infecting the peritoneum. The bowel can be incised at once. This avoids infliction of pain and some shock forty-eight hours later, at which time the bowel is opened by many operators. The artificial anus thus made is then covered with a piece of lint, smeared with sterilized vaseline, and followed by the usual routine treatment of gauze, bandages, etc. The bowels are emptied on the third day and every day thereafter. At the end of a week the silver-wire retention suture is removed. After this time the distal end of the gut may be irrigated with saline or Thiersch solution with an ordinary Davidson's syringe. This prevents accumulation and decomposition of the secretions from the neoplasm of the rectum and affords great comfort to the patient by decreasing pain and tenesmus. Ten days after the operation the patient is allowed to sit up, and may leave the hospital in from two to three weeks.

Excision of the Rectum.

This operation has been practised since the beginning of the nineteenth century. It affords the only hope of effecting a cure in carcinoma of the rectum. The complete removal of the growth and the surrounding tissues beyond the observed carcinomatous involvement is the essential point. Should this be impossible, any local interference by removal of part of the growth is contraindicated, as it aggravates the condition. The operation, then, should be limited to those cases in which the growth is circumscribed, and the rectum is movable on the surrounding tissues. If the mobility of the rectum above the sphincters is impaired, it may safely be assumed that the sacral, pelvic, and mesenteric glands are involved, and no operation will eradicate the disease.

Many methods have been practised by surgeons, but only two operations have attained much popularity. These are the perineal and Kraske operations.

The perineal operation is adapted only to growths confined between the anal margin and the upper borders of the sphincters. After the usual preparation, the patient is placed in the dorsal position, the legs being held by the Clover crutch. The knife enters posterior to the rectum, and an incision is made deep enough to reach above the growth in the rectum, and carried directly back to the coccyx. Two crescentic incisions, one on each side of the anus, are made to join the longitudinal incision, passing completely around the anus and close enough to leave the sphincter, if not involved, in the skin flap. The rectum is then grasped by a heavy vulsellum and dissected out as a whole. This dissection should be carried at least one inch above the point where it is desired to amputate. The male urethra is very close to the rectum; and if it be found necessary to make the incision close to it, a sound introduced into this canal will prevent its inclusion in the incision. The vagina, in the female, is also intimately connected with the rectum, and care must be exercised not to injure it. Hemorrhage is always severe, but can be controlled by gauze packing. The bowel is then divided circularly, grasped with vulsella and brought down as close to the site of the former anus as possible. Catgut sutures are now passed through the edges of the incision and through the wall of the bowel, holding these in apposition. One strong suture should be carried through the side of the incision opposite to the posterior wall of the rectum, through the two outer coats of the bowel and out on the other side. This is attempted in order to gain sphincteric control of the new anus. The rest of the incision should be drained with gauze and allowed to heal from the bottom, as this operation cannot be made aseptic. The sutures are likely to tear out if there is any tension on the bowel. However, it is wise to attempt to form an anus at the natural site. If the parts are kept well cleansed, no worse catastrophe than a slough of the bowel will occur. If subsequent cicatricial contraction occurs at the anus, gradual dilatation will prevent the formation of an impassable stricture. Statistics of this operation vary so much that they are of little value. Kelsey, in 1880, reported a series of 140 collected cases, 118 of which recovered and 22 died, a mortality of about 18 per cent. Six had no recurrence at the end of ten years. Cripps, in 1890, reported 30 personal cases, with 2 deaths, a mortality of about 7 per cent., with 1 case remaining well at the end of nine years.

The Kraske incision, now generally termed the Kraske operation, possesses many advantages over the perineal operation. In the perineal operation the operator works in a funnel, and the deeper the funnel the more difficult it becomes and the more complications are encountered. The field of operation is obscured by hemorrhage, and the control of the bleeding must be left to packing rather than to clamping, thereby destroying all chances of primary union. After the Kraske incision hemorrhage can be controlled by clamps. Judgment can be used in avoiding the arterial trunks, and the whole field of operation is readily seen. No limit is placed on the distance of the disease above the anus. Ten inches can be removed if necessary. Septic absorption is certain to follow the perineal operation, while in the Kraske this may be avoided by attention to detail. The preparation of the patient for the Kraske operation is exceedingly important, as life or death may depend on it. Some surgeons advise as a part of the preparation an inguinal colostomy, as already described, lacking only the formation of the spur. Colostomy, it is claimed, prevents sepsis and overcomes the danger of fæcal wound infection during the weeks of convalescence from the Kraske. But it does not seem necessary or wise to subject a patient to a cœliotomy and three weeks later to a very severe major operation. This delay permits the growth of the carcinoma, taxes the vitality of the patient beyond endurance, and greatly militates against a successful issue of the Kraske. If the patient does recover, a third operation would have to be done to close the fæcal fistula in the inguinal region.

The following preparation is used by Kelsey, whose results have been very good. Four days before operation the patient is given two compound cathartic pills and placed on a milk and meat diet; twenty-four hours later two more pills are given. Twelve hours later the bowel is irrigated with saline solution, and if the movements have not been free and watery, a high enema of salts or castor oil is given. If the stricture is too small to admit the passage of a rectal tube, a catheter is introduced beyond it. On the evening before the operation a pill of opium gr. i., bismuth subnitrate gr. xx., is administered. On the morning of the operation an injection is given of salt solution cleansing the rectum of any remaining fæcal material. This is followed by another pill of opium and bismuth. The patient is taken to the operating-room about six hours after the last injection.

The patient is anæsthetized and placed in a Clover's crutch. The sphincter is thoroughly dilated and the rectum again washed out with a solution of 1:1,000 bichloride of mercury. Care must be taken that none of this remains in the bowel. The rectum is then thoroughly dried with strips of iodoform gauze, rubbed all around above and below the stricture, never using the same piece twice. One piece a yard square is then wrapped up in a sausage-shaped roll, introduced and left in the rectum. The patient is now placed on the stomach in an extended position with pelvis elevated on a pillow. The field of operation is shaved and then scrubbed with a brush and green soap. The whole neighborhood is then scrubbed with an alcoholic solution of bichloride, 1:2,000, followed by ether; again bichloride, and the patient is prepared.

The incision should start just posterior to the anus and extend upwards in the groove of the nates, turning slightly to the left to avoid the coccyx, to a point opposite the posterior superior spine of the ilium. It is usually between six and seven inches in length. In its upper part it should be carried down to the bone at once. The flaps thus made should be dissected back until the lower portion of the sacrum is entirely uncovered. The ligaments connecting the lower sacral vertebræ and coccyx with the pelvis should be divided. A periosteal elevator should be passed under the sacrum to separate the tissues on its anterior surface. This tears away the periosteum carrying the important nerves and the middle sacral artery. The sacrum should then be cut by a heavy pair of bone forceps. It may be divided as high as the third vertebra or lower, depending on the position of the growth. The bone including the coccyx is then removed. This part of the operation should be accomplished quickly. The connective tissue in which the rectum is embedded is next found. The rectum is separated from the surrounding tissues by the finger passed laterally around its anterior surface and out on the other side, separating the anterior attachments. The peritoneal fold is usually easily found by pulling along on the rectum and snipping along its sides with scissors in an upward direction, when this fold comes plainly into view. This accomplished, the peritoneum is opened. If the peritoneum is not divided early, great difficulty will be experienced in drawing the bowel down, as it is held back by this mesentery. Hemorrhage occurring during this period can generally be controlled by pressure. It is unnecessary to clamp the small vessels, as, by the time the rectum is freed from its surrounding attachments, the wound will probably be almost dry. Any large vessels can usually be seen and divided between a double ligature. This dissection should not go too close to the rectal wall, as the blood supply will be affected, and the gut, which is subsequently brought down to take the place of the amputated portion, will slough. An intestinal clamp is then passed over the bowel about one inch above the growth. This closes the lumen of the bowel and prevents the escape of its contents into the wound when it is cut. Towels are placed in the wound covering the whole field except that part of the rectum to be divided. The gut is then cut transversely and the upper end examined to see if any growth remains in it. If not it is surrounded with sterile gauze and given to an assistant to hold out of the wound. The lower and diseased end of the bowel is also surrounded by a towel. The towels in the wound are then removed and the rectum is dissected to the anus. A circular incision around the anus, leaving the sphincter in the skin, is next made. The tumor is then removed and any hemorrhage is stopped by the usual ligature or a ligature on a needle passed beneath the oozing area and tied. The upper end of the bowel is then taken from the assistant and carried down to as near the former anus as possible. If it has not been freed sufficiently from its attachments above to accomplish this, these bands are cut between ligatures until it rests easily in the site of the former anus. There should be no tension on the gut when sutured to the anus, for if there is, it is sure to slough. It is better to make a sacral anus than to have a large sloughing mass of bowel during the convalescence. Occasionally, when the lower two inches of the bowel are not diseased, it may be left and a resection attempted.

This, however, is not attended with much success, as one end of the bowel is covered with peritoneum and the other is not. Failure with a Murphy button is often due to the same cause. The gut should then be sutured at the anus with a number of catgut sutures and the wound closed completely if apposition of the deeper parts can be attained. In most cases it is better to insert a small drainage tube in the upper angle of the wound. An ordinary rectal tube should be placed in the new anus to allow passage of gases and fluid fæces beyond the wound. A collodion dressing is applied about the anus and the rest of the wound is dressed with iodoform gauze. The patient is treated in the same manner as in a routine laparotomy. The bowels are not moved for forty-eight hours. A licorice powder is then administered. The dressings are changed daily in order to observe the local condition. Any rise of temperature or other indication of sloughing or non-union should be followed by irrigation and ample drainage of the wound to prevent general sepsis. The diet is confined to milk and fluid for the first week, then regular diet is allowed.

The patient, in a successful operation, should be out of bed at the end of three weeks. There is no reason why a cure should not be effected by these means if the cases are seen early enough in the disease. Statistics vary. The report of Kraske's own cases, as read before the British Medical Association at Montreal in 1897, is as follows: Eighty out of 110 cases had the radical operation done. There were 15 deaths, a mortality of 18 per cent. In the first 29 cases, there were 10 deaths, a mortality of 34.5 per cent.; while in the 51 later cases there were 5 deaths, a mortality of only 9.8 per cent. Of the 15 deaths, 8 were not from the local effects of the operation.

This mortality list of Kraske shows distinctly the advantage of improved technique in the last fifty-one cases. Kelsey in his own book reports his last seventeen consecutive cases without a death, and later in speaking of extirpation of the rectum for all diseases in the rectum, says that he considers five per cent. about the mortality. It ought to be still further improved, as the only advance in the operative treatment of carcinoma of rectum must be along this line.

Choice of Methods.

A very large number of cases of cancer of the rectum when first seen by the surgeon offer no hope of benefit from any radical operation, and in such cases all that can be done for the relief of patients is colostomy, performed at the proper time. In a certain number of cases, comparatively small, the older or perineal operation will permit of radical removal of the disease. Yet in the majority of cases amenable to operation, the best results are undoubtedly obtained by Kraske's operation.

Comparison of Results of the Perineal and Kraske's Operation.—The mortality of the sacral operation is somewhat higher. Cheyne states that König's mortality is 38 per cent.; Billroth's 34 per cent.; Kocher's 28 per cent.; Iverson's estimate of the Kraske operation is 25 per cent. Czerny's statistics (*Archiv für klinische Chirurgie*, 1894) are very important, as the results of the two methods by the same operator may be compared. Czerny's perineal mortality was 5.4 per cent., while the mortality of the sacral operation was 19.4 per cent. Summarizing results as far as possible, Cheyne estimates the mortality of the perineal operation at 8 per cent., and that of the sacral operation at from 18 to 20 per cent. As regards the results of the perineal operation, Czerny's statistics show that out of 41 cases 3 died of the operation; in 21, or in 51 per cent., early recurrence followed; 8 recurred from seventeen months to five and a half years after the operation (19.5 per cent.); 4 were well after six years (9 per cent.). Of 54 cases operated upon at König's Clinic, 21 died, or 38 per cent. Of 34 cases operated upon more than three years prior to the report, 17 died, or 50 per cent.; 6 had early recurrence, 5 late recurrence, 3 remained well from three and three-quarter years to five years (8 per cent.); 23 were not improved, 8 were improved by the operation. Of these 100 cases Cheyne states that 61 were no better off than if they had been let alone, and not so well off, on the whole, as if they had had colostomy done, for 27 of them died of the operation. Grouping the cases as they applied for relief, Cheyne estimates that not more than 20 per cent. of all patients that come to the surgeon will be benefited by the radical operation. The remainder will fare better if let alone, or with colostomy.

There is a very radical difference of opinion between the English and American on the one side, and the German schools on the other, as regards operative treatment of cancer of the rectum, the Germans operating upon far more advanced disease. Cheyne, representing the English school of surgery, would exclude from the radical operation cases of rapid growth, cases in which the disease forms large masses in the intestines or is deeply ulcerated, and cases in which it has passed through the walls of the rectum and invaded the surrounding parts, as indicated by fixity, or by rapidly growing tumors high up, even though not yet fixed. In none of these is there any real prospect of cure, or even of a marked prolongation of life. In none of these cases is it worth while for the patient to run a considerable risk, inasmuch as colostomy, performed when necessary, not only relieves the patient's suffering, but gives him as long a period of life, with practically no risk.

Cancer of the Pharynx.

In dealing with the subject of cancer of the pharynx, it will be better to make no attempt at separating sarcoma from carcinoma, inasmuch as the two diseases have so much in common from both the clinical as well as the surgical standpoint. It is estimated that sixty per cent. of cases of malignant disease of the pharynx originate either in the tonsil or in the pillars of the fauces. The disease, as a rule, extends upwards rather than downwards. As to the relative frequency of sarcoma and carcinoma in this region, the exhaustive researches of Honsell (Bruns' *Beiträge zur klinischen Chirurgie*, Vol. XIV.) show that carcinoma of the tonsil is more common than sarcoma. Honsell, combining the statistics of Lebert, Wallche, Becker, Sibly, Gerth, and Rapoc, covering different periods from 1830 to 1886, found that, in a total of 30,057 cases of carcinoma, there were 21 cases of carcinoma of the tonsil, or $\frac{7}{100}$ of 1 per cent. In a total of 1,034 cases of sarcoma, only 6 cases of sarcoma of the tonsil were found, or a proportion of 0.6 per cent. To both, sarcoma as well as carcinoma, men are far more susceptible than women; of 32 cases of carcinoma, 94 per cent. occurred in men and only 6 per cent. in women. Of 40 cases of sarcoma, 30, or 75 per cent., occurred in men; 10, or 25 per cent., in women.

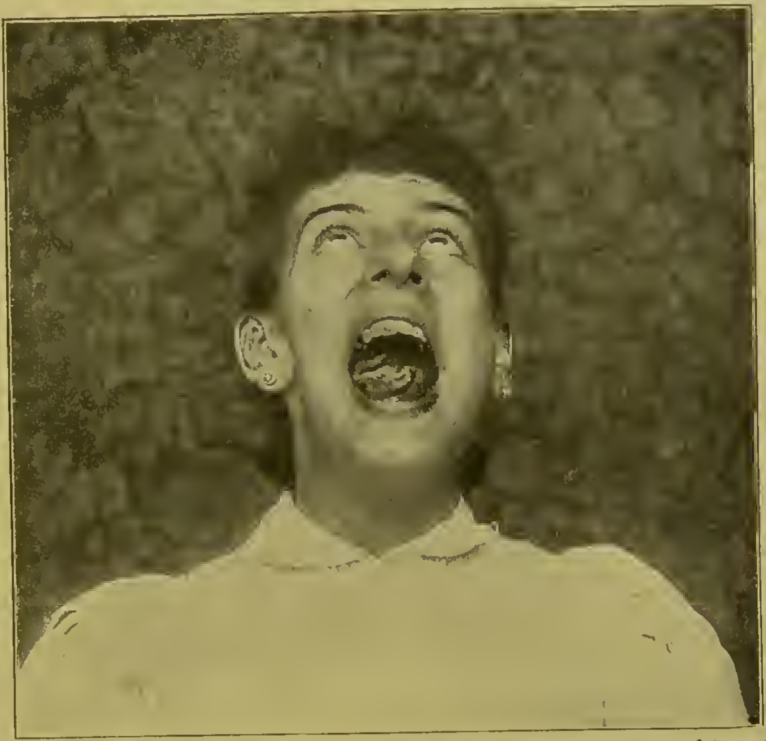

FIG. 6.—Sarcoma of the Tonsil, filling the entire mouth in a woman aged twenty-one years. (Original.)

Age.—Sarcoma of the tonsil occasionally occurs in children, but rarely before the age of twenty, Honsell estimating 15 per cent. only occurring before this age. Of the cases of carcinoma, 70 per cent. occur between the ages of forty and seventy; of sarcoma 55 per cent. occur between these ages.

Symptomatology.—There is perhaps no region in the body in which the early stage of development of malignant disease is attended with fewer symptoms, and this may serve to explain the fact that so many of the cases are inoperable at the time the disease is discovered. The following symptoms are among those most frequently observed in cancer of the pharynx: Tenderness in the region of the throat; feeling of stiffness about the muscles of the pharynx; slight pain in swallowing; the sudden appearance of blood mixed with pus was the first noted in one of Cheyne's cases. In not a few cases the attention is attracted by the presence of a small gland in the neck near the angle of the jaw. In one case reported by Cheyne, a small gland was removed from this region and reported as simple in character, six months before any trouble was discovered in the pharynx.

The chief point of differentiating sarcoma from carcinoma clinically will be found in the relative size of the tumors. Sarcoma in most cases forms a well-marked tumor, projecting into the cavity of the pharynx, whereas a carcinomatous tumor seldom attains large size and early becomes ulcerated, forming cavities of greater or less depth. In both forms of the disease the course is exceedingly rapid, the lymphatic glands being very early affected, and generalization occurring in a very large proportion of the cases.

TREATMENT.

Our knowledge of cancer of the pharynx and of the results of operative treatment has been very greatly increased by the valuable work of Cheyne ("Objects and Limits of Operations for Cancer," 1896). He has made a careful classification of a large number of personal operations, and to these he has added all of the cases that he has been able to collect from medical literature up to 1896. The results of his work in a measure reverse the pessimistic conclusions of Butlin as regards operations for malignant disease of the tonsil and pharynx. Butlin's statistics were based upon 23 cases of malignant disease of the tonsil. Three of these died of the operation; 13 were operated upon from within the mouth, and 10 by external methods, the mortality of the external operation being 20 per cent.; that of the internal, 7.69 per cent. But one case was known to have been well two years after operation.

From a study of these cases Butlin concluded that the removal of the disease through an external incision had proved a dangerous procedure, and the results were not so good as in the operation through the open mouth. He furthermore stated that pharyngotomy could not be recommended, adding that unless the results procured by it are far better for the next series of cases than those it has yielded hitherto, it must be condemned as an unjustifiable proceeding.

The series of cases collected by Cheyne, as I have said, to a certain extent reverse these conclusions. Cheyne was able to collect one hundred and seventy-two cases of operations for malignant disease of the tonsil or pharynx. These operations he classifies into three groups as follows:

1. Cases in which the tumor was removed from within the mouth without splitting the cheek or without preliminary tracheotomy. In this group were 23 cases with 2 deaths, or a mortality of 8.6 per cent.
2. Cases in which there was an external incision in the neck, communicating with the wound caused by the removal of the tumor. In this group were 91 cases with 27 deaths, or a mortality of 29 per cent.
3. This group includes all cases in which the disease involved both pharynx and larynx. In it were 58 cases with 32 deaths, or a mortality of 55 per cent.

Summarizing the final results in these cases, Cheyne found that 30 per cent. were not benefited in group 1; 52 per cent. were benefited; 18 per cent. were doubtful.

In Group 2, 54 per cent. were not benefited, 17 per cent. were, and 29 per cent. were doubtful.

In group 3, 81 per cent. were not benefited, 12 per cent. were, and 7 per cent. were doubtful.

Cheyne believes that these results do not represent the maximum of benefit to be derived from surgical treatment of malignant disease in this region, arguing with much force that we are still in the educational period and that a considerable portion of the mortality as well as the recurrences should be accredited to the so-called *Lehrgeld* that has to be paid in every new field of surgery. The present results, namely fifty-four per cent. not benefited, are but little inferior to the present statistics of breast cancer, and better than the results in rectal and intestinal cancer, all of which are considered suitable cases for operation. If the disease has spread to the tongue, Cheyne believes operation contraindicated. Statistics show that in the fatal cases pneumonia occurs in a large proportion. In those cases in which the larynx and pharynx both are involved, the mortality of fifty-five per cent. combined with eighty-one per cent. not benefited by the operation is a very good reason to make us hesitate to advise operative treatment in this class of cases.

Methods of Operation.—In operations for removal of tumors of the pharynx or tonsils there are two considerations of great importance, the one being ready access to the field of operation, and the other control of hemorrhage.

There is much difference of opinion among surgeons as to the advisability of dividing the lower jaw in order to get access to the seat of the tumor. In many cases division of the jaw is unnecessary and it is clearly advisable to avoid this step if we can attain our object without it. If it is desirable to divide the jaw, Langenbeck's operation, which consists of a simple division of the jaw in front of the masseter, is preferable to Mikulicz's, in which the ascending ramus is completley removed.

Cheyne states that a marked increase in space is obtained by dividing the posterior belly of the digastric and stylohyoid muscles, which permits the jaw and larynx to be pulled forwards on that side to a considerable degree. In four cases by means of a long external incision, splitting the cheek to the masseter, he was able to remove the tonsil, soft palate, and side of the pharynx without division of the jaw.

The control of hemorrhage is greatly facilitated by preliminary ligature of the external carotid artery, yet the risk of secondary hemorrhage has proved so great that Polaillon and Cheyne have concluded to abandon it. Cheyne lost two cases as a result of secondary hemorrhage from the external carotid. The chief danger lies in the fact that the wound, in such prolonged and extensive operations connecting with the cavity of the mouth, cannot be kept aseptic and the secondary hemorrhage is usually the result of suppuration. I believe that it would be well to adopt the suggestion made by Cheyne, to divide the operation into two stages, separated by an interval long enough to escape the danger from any septic influence in the region of the carotid. The method of excision of the carotids of Dawbarn, already described, might be preferable to simple ligature.

Keen has pointed out the great advantage of the Trendelenburg posture in all operations in this region (*American Journal of the Medical Sciences*, June, 1894, and *Annals of Surgery*, July, 1897). It lessens, he believes, the danger of aspiration pneumonia and it renders a preliminary tracheotomy seldom necessary, besides possessing several other minor advantages. The after-treatment of these cases is very important. The wounds should be freely drained and packed with gauze for twenty-four hours.

Cancer of the Face.

The face is peculiarly liable to cancerous infection; far more so than the integument of any other portion of the body. This may be due in a measure to the fact that the face is more exposed. While cancer of the lip is seldom seen in women, cancer of the face is almost as frequent in women as in men. Butlin in a series of 210 cases found that 120 were of male patients and 90 of female. It occurs most frequently after the age of fifty years and seldom before the age of thirty-

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five years. It first appears as a small crack or scaly plaque, or occasionally as a diminutive wart. Butlin believes that in many cases these apparently insignificant starting-points would disappear if let alone, but the irritation caused by frequent picking and rubbing is a factor in bringing about malignant changes. The increase in size is usually very slow, and the disease often runs a course of many years.

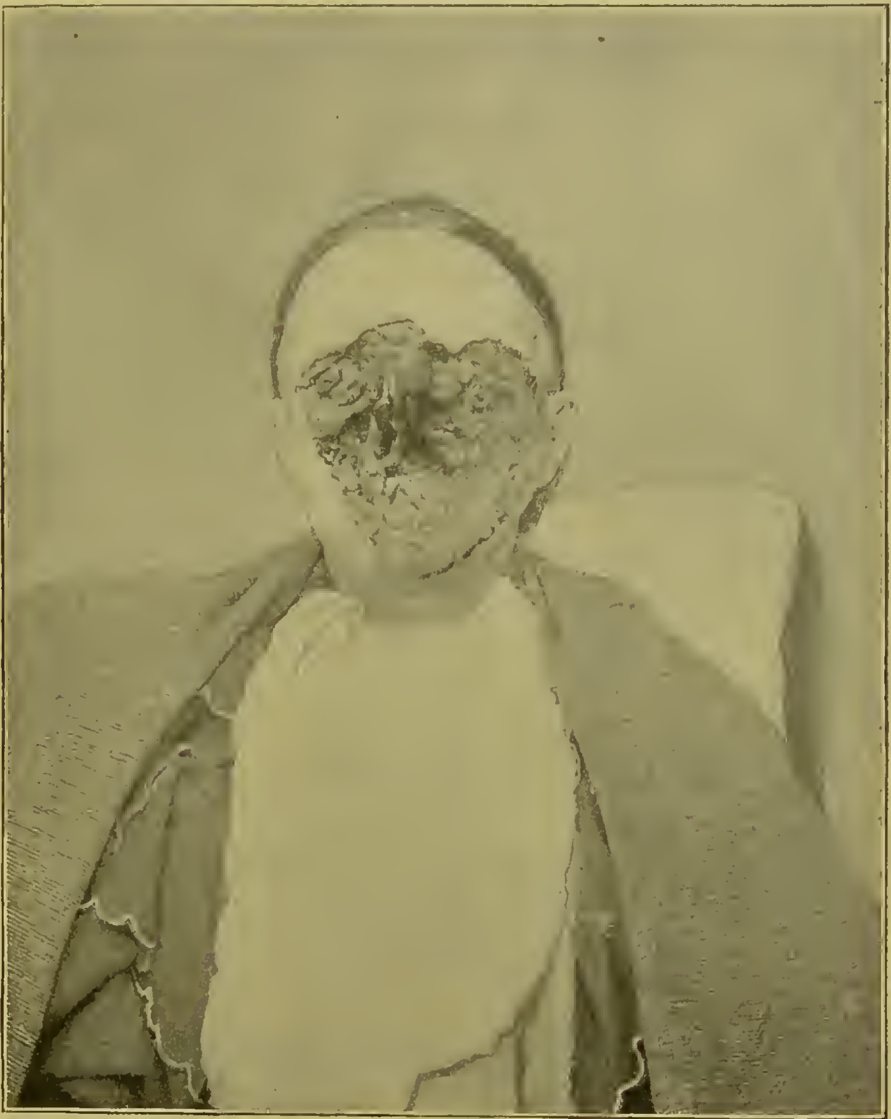

FIG. 7.—Epithelioma of the Face following a Burn. Thirteen years' duration.

The following case is a good illustration, both of the long duration and great extent of area involved in epithelioma of the face:

Miss M——, aged 61 years, was admitted to the New York Cancer Hospital on April 13th, 1896. There was nothing worthy of note in her family history or previous personal history until thirteen years before admission, when she burnt her nose with a hot iron.

The skin came off, but the wound never healed, a small ulcer remaining at the centre of the burnt area. Various methods of treatment were tried, but the disease gradually extended in all directions until the entire face, nose, mouth, in fact all the soft tissues from the chin to the forehead, were destroyed. There was no ankylosis of the jaws; she was able to masticate food, although the process was difficult on account of the absence of the lips. Her condition is well shown by Fig. 7. She died one year later, April 30th, 1897, fourteen years after the beginning of the disease.

Butlin calls attention to a peculiarity of cancer of the face that is seldom found in cancer in other localities, and this is the tendency of the ulcerated area to heal over. The healing is never complete, the healing process often going on in one portion of the cancer and the disease extending in another. In rare cases the disease may be multiple, several areas of infection occurring at the same time.

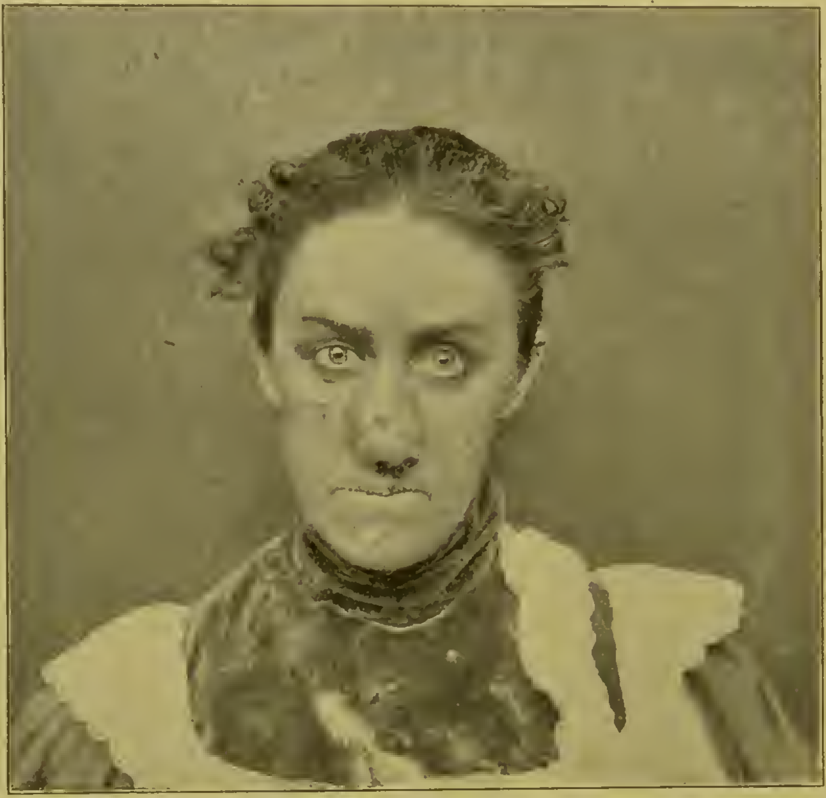

Fig. 8.—Epithelioma of the Nose (before operation).

The accompanying illustrations show the condition before and after operation of an extensive epithelioma of the nose of eight years' duration. Seven partial operations had been performed by another surgeon before I removed the entire nose on a level with the face. The second photograph shows the appearance of the patient wearing a false nose held in place by means of spectacles. The operation was performed about three years ago and the patient is still in good health free from recurrence.

TREATMENT.

Caustics have been extensively employed in the early treatment of cancer of the face. The tendency is to use too mild caustics or to use them with too little thoroughness, hence the results have not been very satisfactory. I believe that a cancer of the face can be best treated by removal with the knife, and certainly the appearance of the patient is much better if this method be employed, inasmuch as a plastic operation can be performed at the same time. The mortality in 206 cases collected by Butlin was 10 per cent. Of 147 cases traced 50 were cured, which proves that cancer in this locality offers the best prognosis of any region with the one exception of the lip.

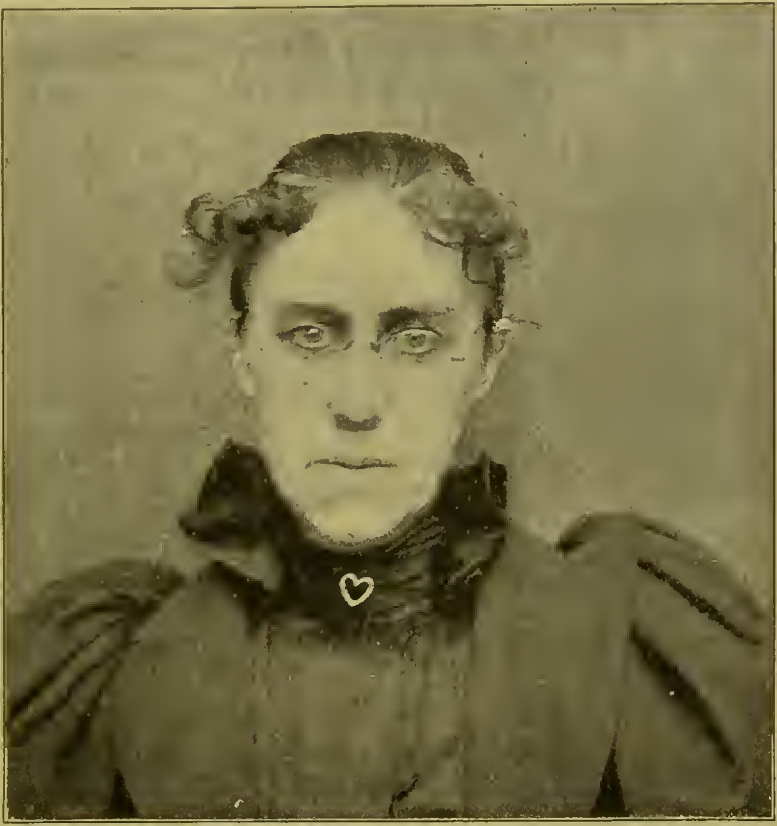

FIG. 9.—The Same as Fig. 8, after operation. (Original.)

Cancer of the Tongue.

Cancer is fortunately less frequent in the tongue than in many other localities, but there is no region in which cancer causes more distress to the patient. The disease most frequently originates along the free border, either at the extremity or on one side. There is frequently a history of origin from the irritation of a carious tooth. In the very early stages, before ulceration has occurred, the diagnosis is not by any means easy. Pain is usually an early symptom, and more acute in character than in most cases of cancer elsewhere. There are certain conditions that often precede the development of cancer of the tongue, and which have been regarded by many as having more or less etiological connection.

Among *exciting causes* may be mentioned leucoplakia and ichthyosis.

Symptoms.—In many cases the disease is not noticed by the patient until the stage of ulceration has occurred. In some instances, however, a small nodule, somewhat indurated and slightly elevated beyond the surface of the tongue, is noticed. In a short time this becomes ulcerated and the characteristic induration appears in the edges. The disease is most frequently found anteriorly, more rarely in the middle third, seldom, if ever, in the posterior third.

Diagnosis.—There are several conditions that more or less closely simulate the early stages of cancer of the tongue, and, in view of the very bad prognosis of the disease, unless operation is performed in the very earliest stages, the importance of a correct diagnosis is apparent. The conditions that simulate the disease are tuberculous, syphilitic, or chronic inflammatory affections. Tuberculosis, I think, most closely resembles the early stages of cancer, and in some instances a most careful microscopical examination may be necessary to differentiate it. A year and a half ago I operated upon a case that illustrates the difficulty that may be encountered in diagnosis.

The patient, a young man 33 years of age, with a history of having always enjoyed perfect health, had first noticed a few months before a small ulcer on the left side of the tongue, about one inch from the apex within the margin. The ulcer was about a half-inch in diameter, had the typical indurated edges, and clinically showed every appearance of an epithelioma. A small piece had been examined by the pathologist to a large hospital, and been pronounced epithelioma. The anterior portion of the tongue was removed. Microscopical examination of the entire tumor by the pathologists of the New York Cancer Hospital, Drs. Dunham and Buxton, failed to confirm the original diagnosis of malignant disease, though numerous sections were made from different parts of the growth. The tissues were then stained and showed the presence of tubercle bacilli. The patient is at present in perfect health, and owing to the fact that the tongue was thoroughly freed from its attachment to the floor of the mouth, he is able to talk almost as well as before the excision.

Senn states that tuberculosis of the tongue occurs, with few exceptions, only in persons suffering from pulmonary tuberculosis. In the patient just referred to there was no family history of tuberculosis, and the patient himself was in perfect health and showed absolutely no signs of pulmonary disease. Senn further states that a tuberculous ulcer is covered by fungous granulations, and lacks the indurated base and margin of carcinoma. This may be true in some cases; but in others, as in the case observed by myself, the indurated margins were well marked and no fungous granulations were present. In other words, the clinical appearance may be absolutely typical of carcinoma, and in such cases I do not believe that the differential diagnosis can be made without the aid of the microscope. In cancer of the tongue, as in other regions, I believe we incur some risk of spreading the disease by removing portions for microscopical examination. I think it would not be a bad plan, in cases in which it is impossible to make an absolute diagnosis from clinical appearances, to remove the entire tumor. If the macroscopical appearance of the tumor, when removed, has not cleared up the doubt, the question of further and more complete operation may be left to a subsequent time, to be determined by the result of a careful microscopical examination of the tumor removed.

Syphilitic lesions may resemble cancer, but in most cases we are able to find evidence of specific disease in the other portions of the body, even if the history is denied. Careful examination of the lymphatic glands in other parts of the body should always be made, if there is a suspicion that the tumor may be syphilitic. Senn states that gumma of the tongue is not infrequently the starting-point of carcinoma.

As regards the *prognosis*, it is unquestionably bad. The disease soon spreads into the muscular tissues and into the nearest lymphatic glands, and this tendency emphasizes the importance of making all operations for the removal of a cancerous tumor of the tongue very radical.

TREATMENT.

The method of operation to be chosen depends somewhat upon the character of the growth. If it be a superficial or warty tumor involving a small portion of the margin of the tongue, or of the upper surface without having invaded the deeper substance of the tongue, I believe that Whitehead's operation should be preferred. If the muscular portion of the tongue is involved—especially the posterior region—better results may be obtained by the method known as Kocher's operation. Whitehead's operation, or the slight modifications of this method, including preliminary ligature of the lingual arteries and removal of the sublingual and submaxillary glands, will, I believe, be found sufficient for the great majority of cases likely to be benefited by surgical interference. Its advantages over

Kocher's method are great. The mortality is much lower, and the wounds are far more likely to heal primarily. Kocher's operation is open to the serious objection that, in dragging the tongue out through the floor of the mouth, it is impossible to prevent the tumor (usually in an ulcerated condition) from coming in contact with the freshly cut healthy tissues, thereby running the risk of new infection. Curtis suggests first removing the part of the tongue containing the tumor through the mouth and then completing the removal by Kocher's method. This I believe to be unnecessarily complicating the operation. The lingual arteries may or may not be ligatured before removal of the tongue. It is a very great advantage, so far as hemorrhage is concerned, first to tie the linguals and, inasmuch as most authorities agree that the sublingual and submaxillary glands should be removed at the time of the primary operation, very little time is lost by tying the linguals, for by enlarging the same incision the glands can be removed at the same time. The tongue should then be strongly drawn out by means of forceps, or better by a stout silk thread passed through it, and cut off at the base by blunt-pointed, straight scissors, having first separated it from its connection with the floor of the mouth. The amount to be removed will depend somewhat upon the situation and extent of the disease. If the cancer covers a very small area, and is situated at or near the apex, a small part of the posterior portion may be left behind. This will enable the patient to articulate fairly well. If the linguals have been tied, there will be very little hemorrhage. I have performed the operation four times. In all of the cases the hemorrhage was very trifling and the patients made uneventful recoveries. After having tied the bleeding points, the interior and posterior surfaces of the stump should be brought together by means of a continuous suture. This completely covers the raw surface, and tends to check whatever oozing there may be; it at the same time lessens the chances of the wound becoming infected.

Waterhouse (Treves' "System of Surgery," Vol. II., p. 520) states: "The operation as performed by Whitehead by means of the scissors is rapidly superseding all other methods and is certainly the preferable operation. Removal of the tongue may be total or partial. When operating for cancer it is in the majority of cases wiser to remove the whole organ." He recommends Kocher's operation only in cases in which the disease has invaded the floor of the mouth and the jaw. With reference to the advisability of removing the entire tongue there is by no means a unanimity of opinion among leading surgeons.

Mikulicz counsels against complete removal except in rare cases, believing that in the cases in which such an extensive operation is indicated the deep lymphatic glands have already become so seriously involved that radical cure is impossible. In regard to Kocher's operation, it is well to call attention to a fact seldom recognized in discussions as to the best method of operating upon cancer of the tongue, and that is that Kocher himself does not advocate his own method in all cases. In his "Text-book of Operative Surgery," 1895, p. 75, he states: "In the case of well circumscribed new growths of the tongue the operation is performed from the mouth after introducing a White's gag, or if necessary after splitting the cheek transversely." He advocates cleaning out the submaxillary fossa at the same time. In extensive carcinoma of the tongue (not so far advanced as to require resection of the jaw) he believes his own method preferable for the following reasons:

"1. Because it gives good access; 2. Because it permits simultaneous removal of the glands as well as all the tissues which intervene between them and the primary seat of the disease; 3. Because it permits of the preliminary ligation of the lingual or external carotid arteries; 4. Because after preliminary tracheotomy the pharynx can be plugged, thus lessening the chances of septic pneumonia; 5. Because of advantages as regards antisepsis."

Kocher adds that of five patients that remained free from recurrence some years after operation three were operated upon by this method.

For a full description of Kocher's method the reader is referred to the work already cited. The technique is in brief as follows: The incision begins below the mastoid process and extends along the anterior border, then turns forwards along the crease of the neck to the middle line and finally upwards to the lower border of the jaw. The flap thus formed is dissected up and fixed with a suture to the cheek. The anterior border of the sternomastoid and anterior belly of the digastric muscle are then exposed. The mass of glands is then raised until the posterior belly of the digastric and the stylohyoid muscles are seen in the lower and posterior part of the wound. The submaxillary gland is then dissected up to the edge of the jaw and removed along with the lymphatic glands.

The facial vessels are then tied, as well as the lingual artery. The mucous membrane is perforated and the tongue drawn out through the floor of the mouth and detached from the hyoid bone. A preliminary tracheotomy is advised in most cases, the anæsthetic being given through the tube. The after-treatment advised by Kocher is to have the wound open, so that the entrance to the larynx may be plugged with moist sterilized gauze, the patient being fed with a tube each time the wound is dressed.

The disease recurs only about one-third as frequently locally as in the glands; Mikulicz reserves local extirpation only for small tumors on the tip of the tongue, in all other cases he advises the removal of the submental and submaxillary glands. He operates by the method I have advocated, first tying the linguals, removing the tongue through the mouth, and suturing the wound at once by sutures placed deeply in the tissues of the stump. He has had no mortality in ten years. He never employs preliminary tracheotomy.

As regards the mortality of the operation, Kocher's results prior to 1882 were 29 cases with 5 deaths, showing a mortality of 17.2 per cent. Between 1882 and 1888, with improved technique, there was 1 death in 28, or a mortality of 3.5 per cent. To show the great variations in different statistics, those collected by Winiwarter in 1878 show a mortality of 42 per cent., while Volkmann had but 2 deaths in 91 cases, or a mortality of 2.2 per cent. Grouping the severe and milder cases together, Cheyne estimates the mortality in the practice of a large number of surgeons to be from 15 to 20 per cent.

As regards final results, actual cures are comparatively rare. Winiwarter's statistics show 2.3 per cent. of cures, with 42 per cent. mortality. König's show 12 per cent. of cures and 28 per cent. mortality. Kocher's show 18 per cent. cures and 10 per cent. mortality. If the subsequent history of Kocher's cases of supposed cures is followed out, in 2 of the cases the cancer recurred ten or twelve years after the operation. One died seven years later of cancer of the stomach, thus reducing materially the number of actual cures. Wölfler estimates that 14 per cent. of Billroth's cases remained well more than nine months.

Butlin's personal statistics (*British Medical Journal*, February 26th, 1898) are the most recent as well as the most complete. Among 102 cases there were 10 deaths. The remaining 92 cases with only 7 exceptions were traced to the final results; of these 20 patients were well from three to twelve years after operation; in 18 cases there was local recurrence and in 28 cases glandular recurrence alone.

Contraindications to Operation.—If the disease extends far back, showing extensive involvement of the muscular tissues of the tongue, or if the glands in the neck are markedly enlarged and fixed, or if the jaw is involved, operation should not be performed. Involvement of the deep gland of the neck, even in a comparatively small cancer of the tongue, should alone contraindicate operation.

As regards palliative treatment, almost nothing can be done to relieve the horrible suffering that accompanies this affection, other than the free use of narcotics. The most troublesome factor of the disease is the constant flow of saliva, and the very great difficulty in taking suitable nourishment. Solid food greatly increases the pain and irritation of the ulcerated area. A cocaine spray and opium internally will give the most relief. I have had excellent results from the use of orthoform powder in painful carcinomatous ulcerations in the nasopharynx and elsewhere, though I have not as yet used it in tongue cases. It is non-poisonous and the anæsthetic effects last from twelve to twenty-four hours.

Cancer of the Stomach.

This subject has been so fully treated by Einhorn in Vol. VIII. of this series that it is unnecessary to more than briefly refer to the operative treatment and results.

Treatment.

The cases in which a total excision of the stomach is indicated are so extremely rare that it is unnecessary here to describe the technique of the operation.

The results of different operations for tumors of the stomach have recently been elaborately studied by Haberkant (*Archiv für klinische Chirurgie*, Bd. LI.), and Krönlein (*Beiträge zur klinischen Chirurgie*, Bd. XV.). In the following tables these results are epitomized.

RESULTS OF THE DIFFERENT OPERATIONS ON THE STOMACH.

According to Dreydorff (*Beiträge zur klinischen Chirurgie*, Bd. XI., Heft 2, S. 333).

Stomach Operations—Mortality.

In Russia.	America.	France.	Germany.	Austria.	Italy.
68.8 per cent.	63.8 per cent.	59.1 per cent.	45 per cent.	45 per cent.	35.3 per cent.

Resection of pylorus : 1883–1894, mortality, 54–80 per cent ;
1885–1894, cancer, 54.4 ; ulcer, 40 per cent.

Typical total resection of pylorus :	1881–1887	62.8 per cent.
	1888–1894	45.1 "

In this series the mortality for carcinoma dropped from 65.4 to 42.8 per cent., and for benign stenosis of the pylorus it dropped from 42.8 to 27.7 per cent.

Mortality of males	64.3 per cent.
" " females	52.8 "

By Haberkant (*Langenbeck's Archiv*, II., No. 51).

	Cases.	Mortality.
Atypical resection of stomach	20	40 per cent.

One case of William T. Bull's was free from recurrence seven months later.

	Cases.	Mortality.
Partial resection of stomach	15	46.6 per cent.
Gastroenterostomy : 1881–1894	298	42.6 "
1881–1887	...	55.9 "
1888–1894	...	39.3 "
Carcinoma	...	47.5 "
Ulcer	...	25 "

Collective Statistics:	Cases.	Mortality.
Resection of pylorus for carcinoma		54.4 per cent.
Gastroenterostomy		43.5 "
Pyloroplasty, 1886–1894	51	21.5 "
As to Age:—Typical total resection of pylorus: under 50 years,	125	50.4 "
" " " " " over 50 "	51	52.9 "
Gastroenterostomy: under 50 years	106	42.4 "
" over 50 "	45	57.7 "

The statistics on pyloroplasty are very imperfect.

	Carcinoma:	Ulcer.
Resection of pylorus	54.4 per cent.	40.0 per cent.
Gastroenterostomy	43.5 "	25.5 "
Pyloroplasty		22.7 "

Peritonitis is the cause of death in about one-quarter the cases of operation on the stomach.

Carcinoma of the Stomach.

1. Report by Krönlein of 67 Cases (Bruns' *Beiträge zur klinischen Chirurgie*, No. 15).

21–30 years	5 patients.
31–40 "	15 "
41–50 "	21 "
51–60 "	18 "
61–70 "	8 "
Total	67 "

The youngest patient was 27 years; the oldest 66 years.

1. Cases not operated on	26
2. Exploratory laparotomy	22
3. Gastroenterostomy	4
4. Resection of pylorus	15
Total	67

Patients who appeared to be operable but who refused operation—7. For 6 of these patients the interval of life between examination by the surgeon and death varied between twenty-seven days and about one year nine and two-thirds months, or an average of about seven months. The report of the seventh patient could not be obtained.

1 *b*. Patients declared inoperable, hence not operated on—19. For 17 of these patients the interval of life between examination by the surgeon and death varied between four days and about eight and one-third months—average about two and a half months.

2. Exploratory Laparotomy, 22 Cases.

No. of Patients.	Interval between Operation and Death.
19	3 days, 1 year 1 month—average 4½ months.
1	Still living end of September, 1895 (4½ months).
2	(?).
Total, 22	

Summing up those in group 1 *b*	17
" " " " " 2 (as inoperable)	19
Total	36

Average duration of life after examination or exploratory laparotomy, 3⅔ months.

Krönlein has hitherto hesitated in advising gastroenterostomy as a severely palliative operation on account of its high mortality, for although Lücke has 7 cases without a death the very complete statistics of Dreydorff show the mortality was 43.3 per cent., and this estimate is closely approximated by Doyen, who found it to be 41.4 per cent.

3. Gastroenterostomy,* 4 Cases.

No. of Patients.	Interval between Operation and Death.
4	3 days, 3 months—average 1 month.

4. Resection of Stomach, 15 Cases.

Number of Patients.	Interval between Operation and Death.
10	1 day, 2 years 2 months—average 8½ months.
5	Still living, November, 1895; average 9 months 9 days.

Two cases died of intercurrent affections and four of recurrence of stomach carcinoma—average 1 year 8 months.

Mortality of operation .... 26.6 per cent.

Operator.	Up to the year.	Number.	Well.	Died.	Mortality. Per cent.
Billroth	1890	29	13	16	55.1
Czerny	1895	16	9	7	43.7
Kappeler	1894	13	8	5	38.4
Mikulicz	1895	18	13	5	27.7
Krönlein	1895	15	11	4	26.6
Total	....	91	54	37	40.6

Cancer of the Uterus.

Cancer of the uterus, as shown by the comparative statistics of Roger Williams, is one of the most frequent causes of death among women over thirty years of age. Kelly ("Operative Gynecology," Vol. II., p. 305) states that of 52 personal cases of epithelioma of the cervix 12 occurred between the ages of thirty and forty;

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* Krönlein says: The reason for my hesitation up to this time concerning this operation was the relative great mortality of this palliative operation up to a short time ago. Not all surgeons have been as fortunate as Lücke, who had success in seven cases without a single death. Death is still just as frequent in consequence of this operation as after the radical resection of the pylorus. A mortality of 40 to 50 per cent., as it is reported by many prominent surgeons and as it is shown by the collective statistics of the last years by Dreydorff (43.3 per cent.), and by Doyen (41.4 per cent.), has been too great for only a palliative operation."

19 between forty and forty-five; 6 between forty-five and fifty, and but 1 in a woman over fifty years of age. These statistics show very clearly that the disease is much more liable to occur during the years just preceding or following the menopause. Kelly also observed 13 cases of adenocarcinoma of the cervix, the most common period of occurrence of this variety of cancer being between the ages of forty-five and fifty. Those cases in which the disease apparently originated in the body of the uterus occurred at a somewhat later period—between the ages of fifty and sixty years in the larger number of cases.

Symptomatology.—The symptoms of greatest importance are a thin, bloody discharge, oftentimes more or less purulent in character, and pain. Neither of these symptoms is particularly well marked in the early stages of the disease. The first thing that calls the attention of the patient to the disease is the presence of this bloody discharge during the interval between the menstrual periods.

The *results of operation* for cancer of the uterus are exhaustively dealt with by Butlin. In 200 cases of supravaginal amputation collected by Butlin, there were 17 deaths, or a mortality of 8.5 per cent. In 341 collected cases of vaginal hysterectomy there were 93 deaths, or a mortality of 27 per cent. More recent statistics (Fritsch and Martin) show a very much lower mortality, only 7 per cent. Abdominal hysterectomy, until recently, was a very dangerous operation. In 148 cases collected by Boussereau there were 106 deaths, or 71 per cent.

As regards final results, of 136 patients operated upon by Braun-Fernwald 33 were well from one to nineteen years after operation; 19 were well beyond three years.

As to the proportion of cures following the vaginal, abdominal, and supravaginal methods, there are no very reliable statistics covering a large number of cases that have been observed beyond three years. Butlin, from a careful survey of the statistics up to 1888, concluded that removal of the entire organ should be limited to those cases in which the disease could not be reached by the supravaginal amputation, and that hysterectomy, when performed, should always be performed through the vagina, the size of the organ permitting it. During the past ten years the method of supravaginal amputation has fallen into disfavor and has been gradually abandoned, vaginal or abdominal hysterectomy having taken its place. In vaginal hysterectomy, the combined statistics of Olshausen, Schauta, Fritsch, Kaltenbach, and Leopold, give 474 cases with 40 deaths, or a direct mortality of 8.4 per cent. The final results of cases of hysterectomy for cancer of the uterus, observed at the Johns Hopkins Hospital (*Johns Hopkins Hospital Reports*, 6, 1895), are most valuable.

In 47 cases the mortality was 10 per cent., 21 patients were still alive, 16 having gone beyond two years in good health. Of the 47 operations 40 were vaginal, 4 abdominal, and 3 combined.

Cancer of the Bladder.

Primary cancer of the bladder is exceedingly rare. It is most likely to originate near the mouths of the ureters. In the early stages it often resembles a papillomatous tumor. It early becomes ulcerated, thus giving rise to hemorrhages.

Symptoms.—Hemorrhage is usually the first symptom, although preceding this there is often an increased frequency in micturition. Pain is generally a prominent symptom and may occur early in the disease; it is more pronounced after the bladder has been emptied. Careful microscopical examination of the urine will often reveal elements of carcinomatous tissue which have become detached by the ulcerative processes and voided with the urine.

The *prognosis* is exceedingly grave, and even with modern improvements in surgical technique there is little hope of bettering the condition.

As to the final *results of operation*, out of 57 cases recently collected by Vendell (*Beiträge zur klinischen Chirurgie*) 24.5 per cent. died within a few days after operation. In the cases in which total extirpation was performed, the mortality was 60 per cent., only 1 patient out of 10 remaining well for any considerable time. This patient (Pawlick's) was free from recurrence eight and three-quarter years after operation. In the great majority of the cases but little benefit followed operation. We must admit that recent results have justified the forecast of Butlin ten years ago to the following effect: "I am not at all sanguine as to the introduction of this operation into the realm of legitimate surgery, but am much more inclined to believe that after it has been performed a few times, or possibly a good many times, it will take its place as a curiosity of surgery with the many other operations for malignant disease that have been introduced during the past few years."

Cancer of the Penis.

Carcinoma is the more common form of malignant disease of the penis, but both carcinoma and sarcoma are comparatively rare. By far the most frequent type is epithelioma. It originates in a small, indurated ulcer which not infrequently is at first regarded as of venereal origin. In some cases it simulates a warty growth, and here again there is the likelihood of confounding it with condylomatous masses. If one can rule out the presence of syphilis, either from a reliable history or from the absence of all other signs, the diagnosis is not attended with much difficulty, even in the early stages. The disease exhibits a strong tendency to involve the neighboring tissues; its course is frequently rapid, as is shown not only by local extension but by the early involvement of the neighboring glands. The pelvic and abdominal glands are often involved soon after the inguinal. Actual metastases in distant parts of the body are, however, not common.

As regards the duration of the disease, this is subject to great variation. I have observed but three cases and in all of these the course was fairly rapid; death may occur in a few months. The average duration as estimated by Demarquay is from two to three and a half years. The collected cases are altogether too few in number to make accurate generalization possible.

TREATMENT.

In view of the high degree of malignancy of the disease in this locality, nothing short of amputation of the entire organ should be advised. If the disease originates in the prepuce and the diagnosis is made very early, a sufficiently radical operation may be possible without amputation. In most cases choice will almost always have to be made between partial and complete amputation. Operation may be performed either with the knife or the galvanocautery, but the knife will practically always have the preference. The chief point to be noted in regard to the technique for amputation with the knife is the manner of dealing with the urethra. The corpora cavernosa should be cut through from the dorsal aspect, the corpus spongiosum being later severed on a plane anterior to that of the first incision, so that when the section is complete the corpus spongiosum projects beyond the rest of the penis. The urethra may be managed in several ways; some advise inserting a catheter, allowing it to remain until the wound is healed. This, however, is not so satisfactory as dissecting out the end of the urethra, drawing it forwards and incising it for a short distance in order to permit of fastening the cut edge to the skin on either side. There is no objection to using a catheter in this case to protect the wound for the first few days. The only advantage that the galvanocautery method possesses is, that it does away with the danger of hemorrhage. If the disease has involved a considerable portion of the penis, complete removal is indicated. This may be done by various methods, among the best of which may be mentioned Gould's (*Lancet*, 1882, I., 821). By this method the scrotum is divided into two halves down to the corpus spongiosum, a large catheter is introduced, the deep end of the urethra is separated back to the triangular ligament, a knife is inserted transversely between the corpus spongiosum and the corpora cavernosa, the catheter is withdrawn and the urethra severed. The deep end of the urethra is then carefully detached and, with the periosteal elevator, the penis is gradually separated from the pubic bone and the crura.

As regards immediate and final *results* of amputation of the penis, in 99 cases collected by Demarquay, the mortality was 4 per cent. More recent statistics of Kaufmann (*Deutsche Chirurgie*, 1886) give a mortality of 10.5 in 180 cases. Of Kaufmann's cases 26 operations were performed with the knife with 1 death; 117 with the galvano-cautery with 16 deaths; 14 died from septic disease; 22 were done with the écraseur with no deaths, showing a very great difference in mortality in favor of the knife or cold wire over the cautery. The number of cases in which the inguinal glands were involved and removed is not stated.

Of 73 cases collected by Butlin from more recent literature the after-history was noted in 32 cases, of which 13 were epithelioma and 19 carcinoma. Of these 32 patients 17 died from causes connected with the operation or from recurrence; 15 were alive and well more than one year after the last operation, 9 of the 15 having passed the three-year limit. Butlin states: "In not one of these cases were the lymphatic glands removed at the time of the primary operation or later. In several instances an enlargement of the gland was noted at the time of the operation, but the swelling gradually subsided after operation. Of 8 cases in which the glands were removed at the time of the original operation, 2 were lost sight of; the remaining 6 died either as a result of the operation or of recurrence."

The duration of the disease in the cases that remained well beyond three years varied greatly, in some of the cases the disease having existed two to three years before operation. Complete extirpation of the organ was performed in only two or three of the successful cases.

Cancer of the Lip.

This disease is much more common in men than in women. Four cases in women were observed by Warren in a total of 73, and the interesting fact is added that 3 of the 4 women were smokers. The disease almost always attacks the lower lip in the proportion of 1 to 20. It generally originates at the junction of the skin and mucous membrane, and is more frequently situated near the median line or a little to one side, seldom being found at the angles of the mouth. Its first appearance closely resembles a little patch of eczema; not infrequently it is mistaken for a crack or fissure due to exposure to the weather. Oftentimes it apparently heals, but on the falling-off of the small scale or scab there is always something left behind, either a slightly indurated area or a tiny speck of ulceration; new scales form and again disappear, but always leaving behind an increasing area of infiltration which after a longer or shorter time assumes the characteristic induration peculiar to cancer. If left to itself, local extension in all directions follows and final involvement of the submental and submaxillary glands ensues. The disease does not run a rapid course as compared with cancer in some other localities, the fatal issue being postponed, as a rule, from three to five years from the beginning of the disease.

Diagnosis.—The conditions that most closely simulate cancer of the lip are eczema, tuberculous disease, chancre, and papilloma.

Eczema lacks the characteristic induration which is present in a measure even in the early stage of cancer. It is more diffuse than carcinoma and the induration is less marked than in a carcinoma of the same size and duration.

Tuberculous disease in this locality is extremely rare, and physical examination of the patient will generally throw light on the diagnosis. In chancre of the lip there will be a history of more rapid development combined with early involvement of the glands of the neck. Papilloma, which is a very rare affection of the lip, can be differentiated by the entire absence of induration. In all cases of suspected cancer of the lip the diagnosis may be easily settled by examination of a small portion removed under cocaine.

TREATMENT.

As regards methods of operation, these depend largely upon the extent of the disease. If the tumor be very small and superficial the removal of a V-shaped portion of the lip, including the neighboring tissues for at least half an inch beyond the edges of the tumor, will suffice. If, however, a larger portion of the lip be involved, it will be necessary to resort to the more extensive operations of which the well-known operation of Malgaigne is perhaps the best. Some authorities urge removal of the submental glands in all cases, whether palpable or not. If this addition be made to the technique, there will probably be an improvement in the final results. In many cases incision must be made to meet the conditions present in the individual case rather than according to any routine method. If enlarged glands be present and firmly fixed, there is little hope of a permanent cure from operation, although the local condition may be made more tolerable.

Immediate and Final Results of Operation.—In operating for cancer of the lower lip of limited extent, there is practically no risk to life. In the cases, however, in which the disease has involved a large portion of the lip, necessitating formidable plastic operations and removal of the glands of the neck, the risk of operation is a factor that cannot be disregarded. Worner (*Beiträge zur klinischen Chirurgie,* 1886, II., 129) collected 896 operations in 62 of which the result was fatal, showing a mortality of 7 per cent.

As to final results, of 277 patients treated at von Bruns' clinic, 106 remained alive and well or had died of some other disease than cancer, more than three years after operation, thus giving a percentage of final successes of 38 per cent. These results are, however, more favorable than those found in the 866 cases collected from various clinics, only 28 per cent. of which remained well beyond three years. Butlin, making a new collection of 424 patients, found 160 well beyond three years, or a percentage of 39, almost identical with that observed at Bruns' clinic. At the New York Surgical Society on April 27th, 1898, Dr. Alex. B. Johnson, of New York, reported the cases of cancer of the lip operated upon at the Roosevelt Hospital during the past six years, 39 in number. The average age of these patients was fifty years, the oldest being seventy-six, the youngest thirty-two. The subsequent history of these cases had been very carefully followed up, and 32 were traced to final results. In 2 of these recurrence took place in the glands of the neck, in 2 the disease recurred locally in the scar, and in 1 in the liver. In 1 case in which the glands of the neck had become involved six months after the primary operation, they were removed, the patient remaining well for three years thereafter. Of the 22 cases traced the average time that had elapsed between the operation and the last report was two and a half years, 5 of the patients having been free from recurrence more than five years, 9 more than three years. Dr. Johnson stated that in almost all of the cases the operation performed was more extensive than that usually employed five or six years ago. He advocated the thorough cleansing out of the submaxillary triangle in every case, whether the glands could be felt or not.

I desire to acknowledge my obligation to Dr. B. H. Buxton, who photographed most of the patients whose pictures are reproduced here, and also to Dr. W. Duff Bullard for assistance in the preparation of the section on cancer of the rectum.

SARCOMA.

(GENERAL PATHOLOGY.)

BY

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Introduction.

I BELIEVE it was John Hunter who said, "Of all things on the face of the earth definitions are the most cursed." Any one who has endeavored to formulate satisfactory definitions for the various classes and sub-classes of neoplasms will, I think, indorse Hunter's opinion; especially when at length he discovers that tumors, like other biological entities, do not admit of strictly logical definition. After all, the genesis, development, and life history of tumors are the really important things to study, and not definitions.

I have elsewhere defined cancer as malignant epithelial (archiblastic) neoplasia; in like manner we may define sarcoma as malignant connective tissue (parablastic) neoplasia. Sarcomata, like carcinomata, are essentially malignant. There is no such thing as non-malignant sarcoma, any more than there is non-malignant carcinoma. It is true that some forms of sarcoma—such as the myeloid—run a chronic course, just as do some forms of carcinoma—such as rodent ulcer, but both alike are very apt to recur after removal, and to manifest other features of malignancy.

We are indebted to the celebrated Johannes Müller for the fundamental conceptions on which the current nomenclature of tumors is based. He first clearly enunciated the important principle that the structural elements of every tumor have their analogues in the embryonic or adult tissues of the normal organism. In accordance with these ideas the different tumors have been designated by adding the quasi-Greek radical "ὤμα" to the name of the corresponding normal tissues whence they originate—*e.g.*, osteoma, chondroma, etc. But this method has not always been rigidly adhered to. In "sarcoma," for instance, we have an exception. This is an ancient term formerly applied to flesh-like tumors (σάρξ = flesh). There was naturally much diversity of opinion as to what should be called flesh, hence the name was very vaguely used. Prior to the discovery of the cell theory, it was commonly employed as synonymous with "fungus."

Virchow is mainly responsible for the rehabilitation of the term, and for its modern significance. He described as sarcomata new formations of the connective-tissue type, distinguishable from the corresponding fully developed tissues by their immaturity, of which the predominance of their cellular elements is a sign. Subsequently they were defined as tumors of embryonic connective tissue, or of some of the modifications that this structure undergoes in evolving the fully developed tissues. In accordance with these ideas Virchow describes fibrous, mucous, glious, melanotic, chondrifying, and ossifying sarcomata. Subsequently more attention was paid to the classificatory value of the form of their constituent cells; hence we get round-celled, spindle-celled, and myeloid sarcomata. The chief features of the disease—so far as these can be expressed in general terms—may briefly be descibed as follows:

Its initial manifestation usually presents as a small, elastic, solitary nodule. Subsequently a more or less distinctly circumscribed tumor is formed, which may have a pseudo-capsule. Such tumors at first tend to push aside the adjacent structures and to waste them by "pressure atrophy," rather than to infiltrate them after the manner of cancers. Consequently relics of the original tissues of the part, such as fatty tissue, etc., are seldom found forming part of the morbid mass, as in cancers. The progress of the disease is generally continuous and fairly uniform; but in certain cases the original tumor, having remained almost stationary for a long period, may then suddenly increase rapidly without any obvious cause. We sometimes see its progress markedly retarded for a time by tough membranes, etc.; but such obstacles once overpassed, the disease extends rapidly.

Sarcomata are usually solid, and they often attain considerable size, in fact the most bulky malignant tumors belong to this species. They may be of firm, fleshy consistence, or soft and medullary. The latter kind is remarkable for its richness in cells, its relatively rapid progress, and its malignant properties. Those of denser texture progress less rapidly, for they contain more formed substance and fewer cells, and it is these that furnish the most bulky specimens. Fortunately, most sarcomata are of this type. Such tumors are much less prone to ulcerative disintegration than cancers, owing to the greater stability of their constituent elements, which are but little prone to degenerative changes.

After a time accessory nodules often develop in the adjacent parts; but lesions of this kind are much less frequently seen than in cancer. It must, however, be borne in mind that sarcomata are surrounded by a zone of latent infection, which usually extends far beyond the obvious limits of the tumor. Hence, unless extirpated in a very thorough manner—with free removal of the surrounding parts—they usually recur locally. This may happen again and again; and yet a cure may be finally effected. It is comparatively rare for sarcomata to disseminate in the adjacent lymph glands; and in this they differ markedly from cancers. General dissemination throughout the body is of commoner occurrence than lymph-gland dissemination; but still it is rarer than in cancer. In advanced stages of the disease cachexia may supervene, and the patients may die of asthenia, as in cancer. In a general way, sarcomata run a chronic course, the average duration of life being considerably longer than in cancer. The spontaneous cure of sarcoma by regression, etc., is as mythical as that of carcinoma. Both sexes are about equally liable; and the disease may arise at any period of life. A certain number of cases are congenital. More are met with in early infancy, especially during the first year, than at any period prior to the twentieth year; after which sarcomata increase in frequency until middle life, becoming rarer again in old age.

These tumors are of much less frequent occurrence than carcinomata—for of 15,481 primary tumors tabulated by me, 54.4 per cent. were cancers, 9.4 per cent. sarcomas, 24.7 per cent. non-malignant tumors, and 11.4 per cent. were cysts. From what has been stated, it will be gathered that there are close analogies between the two diseases—sarcoma and carcinoma—such differences as are noticeable being due to diversity of origin and its consequences, rather than to any essential difference in the nature of the morbid process.

PATHOGENESIS.

In studying the genesis of sarcoma we are confronted at the outset with the same problems that had to be faced in the case of cancer.

Do sarcomata arise through a modification of the formative process; or are they the outcome of the inflammatory process, owing to the presence of microbes or other sources of irritation *ab extrâ?*

It is curious to note how almost every statement that has been made with regard to the presence of microbes in cancer has been paralleled in the case of sarcoma; and in both cases similar conclusions have been drawn. Francke, Lebard, Pilcher, and others have observed various bacteria in sarcomata. Sanfelice, Roncali, Kahane, etc., have met with bodies that they believe to be blastomycetes. In a maxillary sarcoma Toison found oviform corpuscular bodies which he regarded as parasites. Intracellular spore-like bodies have since been described by Pawlowsky, Clarke, Vedeler, and others, and are regarded by them as parasitic protozoa. Finally, Moty claims to have found a very small micrococcus in the blood of sarcoma patients. All the above-mentioned workers believe the bodies they have observed to be the specific cause of the disease. It is not necessary to confute these claims in any detail, as their untenability is now generally recognized. Suffice it to remark that before a disease can properly be called parasitic, the parasite must be found and isolated, and the disease it is alleged to cause must be reproduced by its inoculation. It cannot be affirmed that these postulates have been fulfilled by any of the alleged sarcoma microbes. Neither can it be said that the attempts lately made to prove the contagious and infectious nature of sarcomata have been at all convincing. The disease cannot be transmitted from one human being to another by inoculation; nor is it transmissible by any less direct method. There is no evidence of sarcoma being a "water-borne". disease. Such phenomena as "sarcoma epidemics," "sarcoma houses," and "sarcoma à deux," have been imagined, but not demonstrated.

Like cancer the disease is probably autoinoculable. Nicaise has reported an instance of sarcoma of the abdominal wall which began in the track of a puncture, made into a uterine sarcoma, under the supposition that it was a cyst. In a man of fifty-five, with an eroded melanotic tumor of the left lower eyelid, Venneman found that a similar tumor had developed on the corresponding part of the ciliary border of the upper eyelid, where this came in contact with the primary tumor. Such occurrences suggest that, under favorable conditions, the disease may be spread by "contact infection." Probably also wounds made for the removal of such tumors may be inoculated by the traumatic dissemination of particles of the morbid structure.

Of the many attempts that have been made to transmit human sarcoma to the lower animals by grafting, etc., the results have almost invariably been negative. Curtis, however, claims to have succeeded in transplanting a fragment of myxoma from a young man's thigh into a rabbit, where, in the course of twelve days, it originated a tumor the size of a small orange. Both tumors are said to have teemed with microbes resembling the yeast fungus, which the author names *megalococcus myxoïde*. Many years ago Weber injected a magma derived from a soft sarcoma of a man's upper jaw into the veins of the thigh of a dog, and a fortnight afterwards he found that a large sarcomatous tumor had developed there. These cases would be more conclusive if a longer interval had been allowed to elapse after the inoculation, so as to insure the subsidence of the local inflammatory reaction, which might easily be mistaken for sarcoma. Moreover, other experimenters have found that the tumor-like swellings at first formed have quite disappeared some weeks later. A similar objection applies to most of Juergens' results of the implantation of human melanotic sarcoma into the peritoneal cavity of rabbits. Some of his later experiments are, however, free from this objection. Thus, having implanted particles of metastatic human sarcoma into the peritoneal cavity of a rabbit, he found a tumor the size of a nut in the right eye, three months afterwards. In another rabbit, similarly treated with myxosarcoma of the human ovary, tumors were found in the lungs and intestines, when it was killed some months after the operation. These experiments are interesting but by no means conclusive, for there are many fallacies, not easily excluded, to be guarded against.

Attempts to transmit the disease from one animal to another of the same species have nearly always been abortive. Only Eiselsberg claims a success. He grafted portions of a fibrosarcoma from the back of one rat into the peritoneal cavity of another, and a large pseudosarcomatous tumor soon afterwards developed at the seat of implantation. Richet found that intravenous injections of the pulp of non-ulcerated sarcomata caused no toxic symptoms of any kind. These experiments have revealed nothing in the least resembling the phenomena resulting from the inoculation of infectious disease. The results attained are more like those met with in tissue grafting. Hence it may be inferred that the constituent cells of sarcomata are themselves the sole disseminators of the disease, and that in them resides the essence of malignancy.

Long before the discovery of microbes, even before the announcement of the cell theory, malignant disease had been regarded as an outcome of chronic inflammation and irritation. This view of the subject is especially associated with the name of Broussais, its most brilliant exponent, who considered that any form of chronic irritation might originate the disease. For the present it will suffice for me to point out that lesions of this kind cannot be regarded as the *necessary* antecedents of sarcoma, since in the great majority of cases the outbreak of the disease appears to be entirely spontaneous. To borrow a Darwinian simile, these lesions play but a subordinate part in causing any particular outbreak: "Like that which a spark plays when a mass of combustibles bursts into flame, the nature of the flame depending on the combustible matter and not on the spark."

Thus of 34 cases of sarcoma (15 of the female breast and 19 of the upper jaw), in which special inquiries were made by me as to pre-existing injury or disease of the part, there was history of such conditions in only 6 cases, or 17.6 per cent.; in the remaining 82.4 per cent. the disease appeared to have arisen without any obvious extrinsic cause. With regard to the influence of traumata in the causation of sarcoma, I must refer the reader to what I have previously stated when treating of cancer. For reasons there set forth it appears that such stimuli are of themselves incapable of originating the disease.

Nevertheless, there are some exceptional cases in which the "spark-like" action of traumata in precipitating the formation of sarcomata is very marked. Thus, under the heading of "acute traumatic malignancy," instances have been reported by Barwell and others of sarcomata rapidly developing after severe local injuries; and, after the incomplete removal of sarcomatous tumors, very rapid local recurrence may sometimes spring up in the unhealed wound. In this connection, mention may be made of the "callus-sarcomata," in which the disease appears to spring from the reparative new formation, as in cases reported by Haberen, Pollard, and others, and also to the "sarcomata of scars," which constitute one form of keloid. In such instances the final outbreak is but the explosion of a long train of antecedent preparation; hence the failure of attempts to reproduce similar results experimentally in animals.

We now have to consider the connection between the genesis of sarcomata and certain developmental flaws to which Cohnheim has especially called attention. Long before Cohnheim's time the proneness of certain congenital defects to originate sarcomata had been recognized by pathologists, especially by Paget, Pemberton, and Virchow. Of thirty-four cutaneous melanomata tabulated by Pemberton (1858), no less than fifteen arose from congenital warts, moles, nævi, or other blemishes. Even as far back as 1853, referring to the proneness of melanomata to arise from pigmented moles, Paget said: "It seems a striking illustration of the weakness in resisting disease, which belongs to parts congenitally abnormal." In another passage he adds: "This peculiarity may make us suspect that there may be other, though invisible, defects of first formation in our organs, which may render them, or even small portions of them, peculiarly apt for the seats of malignant and other specific diseases." Virchow subsequently developed the subject still more fully, showing that sarcomatous tumors of the skin often developed from congenital soft warts (verrucæ molles), nævi materni, moles, and other congenital anomalies.

Under these circumstances, it seems unreasonable for the admirers of Durante to claim for him the authorship of the embryonic theory of tumors, because he published in 1874—one year before Cohnheim's "Manual" appeared—a brochure on "The Physio-pathological Connection between Maternal Nævi and the Genesis of some Malignant Tumors." Paget and Virchow have never advanced such claims, although they are far more entitled to do so than Durante. The truth is, for those who were acquainted with the works of Paget and Virchow there was nothing new in Durante's publication. The credit of elaborating the indications furnished by these observations into a comprehensive theory of tumors undoubtedly belongs to Cohnheim. He seems to have founded his celebrated theory mainly on a case of renal myosarcoma that he observed in an infant sixteen months old. In the left lumbar region there was a large tumor, to which the remains of the left kidney—otherwise unaltered—were adherent. Within the capsule of the right kidney, at its upper end, there was also a rounded, circumscribed tumor, quite distinct from the kidney substance. Both tumors were sarcomata, containing striped muscle fibres. It seemed evident that tumors thus circumstanced could only have arisen from heterotopic elements detached from their normal connections during embryonic life. Hence he concluded that all tumors thus originated. At first very few facts could be adduced in support of this bold speculation. The possibility of such an amount of developmental irregularity as it presupposed was then generally disbelieved. The light of modern science has, however, effectually dissipated this misconception, and our eyes have been opened to the hidden defects of normality. Sequestrated fragments of the various tissues and organs have now been found to exist in every part of the body that has been specially examined for them. In short, it is evident that in the course of ontogenesis innumerable fragments are thrown off, which, as development proceeds, become embedded in the tissues, where, as a rule, they remain quiescent ever afterwards. It is to belated structures of this kind that the term "rests" is applied. My conception of the significance of this term differs somewhat from Cohnheim's. He thought that "rests" consisted solely of embryonic tissue, which, after sequestration, lay dormant in the body without undergoing any further developmental change. If "rests" of this kind really exist, their entity has yet to be demonstrated. The "rests" with which histology has made us acquainted always present indications of having undergone more or less developmental exegesis along the lines proper to the parental tissue. Again, Cohnheim thought that "rests" originated solely during embryonic life; but it has now been ascertained that similar sequestrations arise also during post-embryonic life.

What part, if any, do structures such as these play in the genesis of sarcomata? In answer to this question I must say that I have been greatly impressed with the large proportion of the sarcomata of early life arising in connection with congenital anomalies of this kind; and even among the sarcomata of adult life I have met with many such cases. In the following pages I shall have occasion to refer more in detail to this subject.

Virchow divided tumors into the histoid, organoid, and teratoid. Among the histoid tumors, which consist of a single primordial tissue or its derivatives, he classed the sarcomata. In a considerable number of cases, however, sarcomata have been found containing teratoid and heterotopic structures, evidently not derived from a simple histoid matrix. Most of these mixed tumors obviously arise in connection with embryonic developmental disturbances. It has been urged by Ribbert that the origin of tumors from "rests" depends less upon the embryonic characters of the originating cells than upon separation from their normal connections. However this may be, such cells are rich in nuclear substance, very prone to mitoses, and also rich in glycogen, all of which are characteristic features of embryonic cells.

Among the innocent congenital malformations, in connection with which sarcomata have been observed to develop, the teratomata must be mentioned. Many such cases have now been reported by Montgomery, Kirmisson, Czerny, Virchow, Jores, Wernitz, Keller, Emanuel, Lazarus, Biermann, Ewald, and others. Instances of the sarcomatous degeneration of ovarian dermoid cysts have been described by Jacobsen, Hauke, Doran, and others. In the neck a similar association has been observed, of which Samter has recently reported an example. In the kidney Hildebrand has described an instance of sarcoma arising in connection with abnormal union of its cortical and medullary segments. According to Garré and Goldmann multiple sarcomata of the nerves arise in connection with defective development of the nerve sheath.

Probably most gliomata also originate in connection with similar developmental defects. I have seen a young man, the subject of multiple exostoses since childhood, in whom a large sarcoma developed from one of the exostoses on the ilium. Chiari has reported a similar case. I have had under my observation a single woman, aged forty-nine, in whom a small spindle-celled sarcoma developed from a microphthalmic eye; the tumor was of five years' duration. Many similar cases have been reported. I know of several instances in which sarcomatous and myxomatous tumors have arisen from sequestrated mammary glandular structures in the vicinity of the mamma.

The origin of certain peculiar forms of sarcoma that grow from the lower part of the uterus, with whose structure various heterotopic elements, such as cartilage, bone, striped muscle, etc., are blended, as in cases described by Pernice, Rein, Thiede, and others, may with tolerable certainty be referred to germs sequestrated from the matrix of adjacent tissues during early embryonic life. Hence it seems certain that sarcomata have a special tendency to arise in connection with certain developmental defects.

The question now arises as to whether the constituent cells of such defective areas are the *only* ones capable of originating sarcomata, as Cohnheim maintained. It appears to me that such a proposition is in the highest degree improbable. On the contrary, there are good reasons for believing that sarcomata may arise whenever undifferentiated cells are present, and that they are most prone to arise where such cells most abound.

A good deal of attention has lately been directed to certain malignant tumors that appear to arise from the residua of placental structures, remaining embedded in the uterine musculature after parturition. Some of these growths consist chiefly of decidual (maternal), and others of chorionic (fœtal) structures. Sänger, one of the first to study these tumors, gave them the name of "sarcoma deciduocellulare." It has been much discussed whether they are of epithelial or connective-tissue origin. If the current views as to their pathogenesis be correct, the part played by post-embryonic "rests" in their origin is a very interesting and remarkable one.

In the genesis of sarcomata, as in the genesis of cancer and other organic structures, I believe we must take into consideration two factors: the *cells* whence they originate and the *force* that regulates the cellular activities. The essence of the process is that certain cells of the affected part grow and multiply more rapidly than their congeners. I regard this rejuvenescence as due to failure of the integrative force that normally restrains their activities within proper limits. Thus the process by which sarcomata arise may be regarded as a kind of abnormal gemmation; the tumor being the result of a modified superinduced repetition of the developmental process. Hyperplasia of the tissue elements, and not inflammation, is the starting-point of every sarcoma. Hence the genesis of sarcoma is a phenomenon of the same order as discontinuous growth in general. Thus sarcomata differ from carcinomata only in that they arise from a different type of tissue element.

Histogenesis.

Sarcomata may arise wherever structures of the connective-tissue type, containing cells still capable of growth and development, exist; and they are most prone to arise where such elements most abound. Thus few parts of the body are exempt.

At an early period of embryonic life, those parts where connective substances will subsequently arise, are composed solely of closely aggregated parablastic cells. These cells are nothing but small, rounded masses of nucleated protoplasm. Such is the embryonic parablastic tissue, whence any kind of connective substance may subsequently develop. In passing to a higher stage of organization, these cells become changed in shape and otherwise modified. In man and the higher animals immature structures of this kind have normally only a transitory embryonic existence; but the *sarcomata* consist mainly of them. In the arthropoda and mollusca such structures have a permanent existence.

In the evolution of mature connective tissues from this cellular embryonic structure, the cells become separated from one another by the differentiation of intercellular substance. A distinction thus arises between the cells which form, and the intercellular substance which is formed. Thus, as development proceeds, most of the embryonic cells are used up and converted into special tissue. Many cells seem totally to disappear, or only their nuclei are left. In certain localities, however, a considerable number persist—embedded in the intercellular substance where they are still capable of active development. Under ordinary circumstances such cells simply concern themselves in maintaining the normal structures; but under certain pathological conditions, they become the germs whence the various parablastic neoplasms originate. Thus the various kinds of sarcomata arise. These neoplasms are composed mainly of parablastic cells, which are either rounded or spindle-shaped. The new formation seldom advances much beyond this low grade of organization, which is closely allied to that of embryonic parablastic tissue. All neoplasms thus constructed are more or less malignant.

In addition to the cellular embryonic form of connective tissue, gelatinous, fibrous, calcareous, fatty, cartilaginous, osseous, and other special varieties have been recognized, each of which may be present in sarcomatous tumors.

The formation of *gelatinous* from embryonic tissue takes place by the differentiation of soft, hyaline intercellular substance containing mucus. In this the cells are sparsely embedded; they may be of rounded shape, when they are generally isolated, or stellate, when they usually communicate by fine protoplasmic processes. This tissue is permanent in many of the lower animals, such as mollusca and medusæ. In the human embyro it is very abundant, existing wherever fibrous or fatty tissue will subsequently be formed as in the subcutaneous tissues and in the medulla of the bones. At birth it is found in the umbilical cord, and it is permanent in the vitreous humor of the eye. Pathological new formations thus constituted are the *myxomata*. Such neoplasms originate from the cells of the parablastic tissues, especially the fibrous, cartilaginous, and fatty. These proliferate and produce embryonic parablastic tissue, whence the gelatinous tissue subsequently differentiates as in the embryo. Myxomata are a degree higher in organization than sarcomata. They represent immature fibrofatty tissue, and are therefore slowly organized. Such neoplasms are apt to recur locally; and occasionally they give rise to metastases.

Fibrous tissue may be regarded as a further development of gelatinous tissue. In the process of evolution the diffluent, mucin-bearing, intercellular substance gradually fibrillates and solidifies and is converted into gelatin. Many histologists describe fibrous tissue as originating without a gelatinous transformation—the developing cells (fibroblasts) arranging themselves into compact masses of which the protoplasm fibrillates. In the developmental process the cellular elements gradually waste and disappear. However, here and there considerable numbers remain embedded in the fibrillar intercellular substance. It is from the abnormal proliferation of these cells that fibrosarcomata arise, the steps of the process being analogous to those of normal development. Fibromata have a similar origin, but their development is more complete. Many chronic forms of fibrosarcoma contain so much fibrous tissue as to obscure their sarcomatous elements.

Fatty tissue is but a modification of ordinary areolar tissue, owing to the deposition of fat within its cells. The panniculus adiposus of the adult is in the fœtus a gelatinous tissue. In its evolution fatty tissue passes through the cellular and gelatinous stages; but while fibrillation is still incomplete, the cells form groups and fat accumulates within them. The accumulation of fat within the cell causes the nucleus, with the little remaining protoplasm, to be pressed against the cell wall. These cells are, however, still capable—under pathological conditions—of taking on fresh activity. Embryonic parablastic tissue is thus formed, which develops into fatty tissue, as in normal evolution. When, however, the process falls short of this a mixture of immature fatty tissue with myxomatous and sarcomatous structures is the result.

Cartilage is developed in the embryo from cellular parablastic tissue by the formation of firm, chondromatous, intercellular substance. At first this is scanty, and the tissue consists almost entirely of cells. This is the so-called cellular cartilage, which is permanent in the vertebrate notochord. As development proceeds the cells multiply, and each new cellular group forms round it fresh chondromatous substance. This, which is at first homogeneous, may remain so, as in hyaline cartilage, or it may undergo further differentiations, whence the fibrous and elastic varieties. Cartilage readily passes into gelatinous, fibrous, or osseous tissues. These metamorphoses may be effected directly, as when cartilage arises from the perichondrium, periosteum, or marrow; or indirectly through the intermediate stage of embryonic tissue, as in the formation of bone. Cartilage cells are, as a rule, spherical, and they are quite detached and separate from the intercellular substance in which they are embedded. In many selachians and cephalopods, however, a kind of cartilage is met with in which the cells communicate freely by fine radiating processes. This form does not occur as a normal production in man, but it is sometimes found in chondrosarcomatous tumors. Similarly calcified cartilage, which in man is normally only a transitory structure, is often met with in chondromatous new formations; and in sharks it forms a persistent part of the skeleton. Chondromatous new formations mostly arise in connection with skeletal structures or their derivatives. The matrix tissue may be preëxisting cartilage, perichondrium, periosteum, marrow, bone, or other connective substance. Such neoplasms never develop directly from any adult structure; but the parablastic embryonic tissue is first formed, and the subsequent evolution is often the normal type. When this is incomplete, chondrosarcomata arise; which, according to their degree of immaturity, are more or less malignant. Even in such cases, in portions of the tumor, fairly perfect cartilage may be evolved.

All *bone*, whether of embryonic or postembryonic origin, is evolved from the so-called osteogenetic tissue, which consists of small protoplasmic cells (osteoblasts). These secrete the sclerogenous substance, which forms the essential constituent of bone. Each osteoblast contributes a zone of osseous matrix, in the centre of which it becomes embedded, developing fine processes which communicate with other adjacent cells. Thus the so-called bone corpuscles arise. The osseous substance is at first a soft, fibrillar kind of connective substance, which gradually hardens owing to impregnation with lime salts. The development of bone is often preceded by that of cartilage and fibrous tissue. In the latter case, ossification is effected by conversion of the connective-tissue cells into osteoblasts, while the fibrous intercellular substance disintegrates. The development through cartilage is the more frequent, and it holds for most of the vertebrate skeleton. In this process the cartilage disappears partly by retrogressive changes and partly by transformation into marrow and bone. Here metaplasia precedes the osteoblastic process. Bones increase in thickness at the expense of the cellular layer of the periosteum, which originates the osteogenetic tissue whence the new bone is developed. Ossifying tumors generally arise from skeletal structures or their derivatives, such as periosteum, perichon-

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drium, cartilage, bone, marrow, and fibrous tissue. The cells of the part whence such a tumor is forming proliferate, and finally develop into bone, as in normal evolution, either directly or indirectly through fibrous tissue or cartilage. When the development is complete osteomata are formed. Ossifying sarcomata arise when the neoplastic new formation falls short of this goal.

It will be gathered from the foregoing that malignant and non-malignant parablastic neoplasms are connected by numerous intermediate transitional forms; and cases are not infrequently met with in which it is difficult to determine to which variety the tumor belongs.

According to Ackermann, the origin and increase of sarcomata are intimately associated with the blood-vessels of the part. He describes sarcomata as consisting of interwoven, anastomosing, fasciculated bundles of cells and fibrillæ, the axis of each fasciculus comprising a capillary blood-vessel lined by endothelial cells, external to which the essential elements of the tumor develop. It is certainly chiefly by perivascular extension that the disease spreads.

PATHOLOGICAL ANATOMY.

The morphological characteristics of sarcomata and their biological properties are largely determined by the nature of their constituent histological elements. In their turn these are powerfully influenced by the nature of the matrix, which varies in different localities. Notwithstanding these local diversities certain types of sarcomatous tumors may be recognized as common to all parts. Sarcomata being essentially cellular may be classified according to the nature of their elemental constituents of which the chief varieties are round, spindle-shaped, and myeloid cells. Any given tumor always contains more than a single variety of cell; but in most sarcomata some special variety predominates, and after it the tumor is named. Round-celled and spindle-celled forms are the commonest, but a mixture in which both these varieties are dominant is of frequent occurrence. The constituent cells of sarcomata are not massed together in a pseudo-alveolar structure, like those of carcinomata, but each cell is embedded in more or less intercellular substance of fibrillar, mucoid, or diffluent nature.

Sarcomata are rich in blood-vessels, the vascular channels often being separated from the tumor elements by nothing but the endothelium of the intima, and in the softer tumors even this may be absent. Hence detached elements easily enter the circulation and disseminate the disease in distant parts of the body. According to Young, nerves accompany the blood-vessels.

Round-celled sarcomata present as soft, rapidly growing tumors, of encephaloid or medullary aspect. They usually consist of small round-celled structure, identical with the embryonic parablastic tissue. Their constituent cells are markedly rich in glycogen and nuclear substance, and they originate mitotic changes with great frequency, asymmetrical and multiple figures being very common. Intercellular substance is scanty, and it is usually diffluent or fibrillar. Such tumors are highly malignant. They may arise from any part of the body, but their commonest seats are the bones, brain, retina, kidney, lymph glands, etc. Occasionally sarcomatous tumors consisting mainly of large rounded or ovoid cells are met with; they are less malignant than the small-celled form.

Spindle-celled sarcomata consist of closely packed, elongated, fusiform cells, having a fasciculated arrangement, as if the cells formed a sheathing to the blood-vessels. They usually manifest a marked tendency to fibrillation. Hence these tumors often resemble fibromata in their general aspect. They are the commonest form of sarcoma. Small and large celled varieties are met with. The former are more malignant than the latter. Generally speaking, spindle-celled sarcomata are less prone to disseminate than the round-celled form; but they are exceedingly apt to recur. Their seats of predilection are the bones, skin, choroid, breast, and connective tissue.

Myeloid sarcomata are distinguished by the predominance of very large multinucleated cells, such as are normally found in the young marrow and in other localities. These impart to the tumors their characteristic maroon-reddish aspect. Myeloid sarcomata mostly originate in connection with the medulla of the bones; but instances have been reported of typical myeloid tumors arising from parts quite unconnected with the skeleton, such as the mamma, uterus, skin, etc. Myeloid sarcomata are the least malignant tumors of their kind. They are, however, apt to recur locally and to invade adjacent structures, and instances of their dissemination have been reported.

Under such names as "alveolar sarcoma," "plexiform angiosarcoma," "cylindroma," "perithelioma," "endothelioma," etc., certain rare tumors have been described, which in their structural feature and in their properties are more like carcinomata than sarcomata. They are believed to arise from endothelial cells of blood-vessels, lymphatics, etc. Recent researches seem to indicate that the endothelium is a derivative of the archiblast rather than of the parablast; so, if we accept this view of their origin, these tumors should be classed with the carcinomata. At any rate, like the latter they disseminate locally, invade the adjacent lymph glands, and cause metastases. Moreover they recur locally, and are highly malignant. Tumors of this kind have been met with in the ovary, superior maxilla, mamma, uterus, skin, orbit, parotid, pleura, peritoneum, omentum, etc.

Notwithstanding the comparatively circumscribed forms that sarcomata usually assume, they have a great tendency to invade the adjacent structures, either continuously or discontinuously. In removing them it must be borne in mind that the disease always reaches far beyond the apparent limits of the tumor. Perivascular extensions of the growth spread out into the contiguous structures; and if these are not removed, recurrence is sure to ensue. It is these perivascular extensions that originate most of the accessory nodules, that arise in the vicinity of sarcomatous tumors. Owing to the close relationship of the tumor elements to the blood-vessels, as previously mentioned, these readily find their way into the circulation; and so produce metastases in the lungs, liver, kidneys, brain, etc. Sarcomata rarely disseminate in the adjacent lymph glands, probably because so few lymphatics enter into their composition. Indeed the very existence of lymphatics in these tumors has been denied by some pathologists.

Sarcomata are much less prone to degenerative disintegration than carcinomata; hence when they project on free surfaces, instead of excavated ulcers, eroded fungoid outgrowths usually present. Sarcomata that arise in glandular organs, or in the immediate vicinity of such structures, generally contain epithelial elements derived therefrom, in connection with which cysts—often with intracystic growths—arise (*adenosarcoma*), as in the breast and parotid. Other sarcomata contain blackish (*melanoma*) or greenish (*chloroma*) coloring matter. The former are commonest in connection with the skin, eye, rectum, etc., and the latter usually arise from lymphadenoid structures.

Although the initial manifestation of the disease usually takes the form of a solitary nodule, yet in certain cases it from the first presents a diffuse infiltration. Moreover, it may be multiple *ab initio* or even symmetrical (*e.g.*, in the breast, ovary, etc.). Multiple sarcomata, primarily arising, have a marked tendency to affect the same tissue in different parts of the body, *e.g.*, the bones, skin, etc. Occasionally the disease coexists with cancer or with non-malignant tumors.

The Initial Seats of Sarcomata.

In infancy and early life the localities especially prone to be affected are very different from those whence the disease is apt to arise at later periods. Picot's analysis of 424 sarcomata in infants shows that the initial seats of the disease were as follows: Eye and its annexes in 100 cases, kidney in 80 cases, bones in 67 cases, brain and its membranes in 31 cases (dura mater 8), abdomen and pelvis in 19 cases, testes in 15 cases, liver in 13 cases, prostate in 8 cases, skin in 8 cases, intestine in 7 cases, neck, tongue, and ovary each in 6 cases, etc. At this early period both sexes are about equally liable.

At later periods of life I have ascertained that the parts chiefly affected are the bones, especially the superior and inferior maxillæ, the femur, humerus, tibia, innominate, scapula, and skull bones. Next to the bones come the female breast, genital glands, eye, parotid, and skin. Sarcomata also frequently arise from the face, neck, thigh, leg, orbit, etc.

My analysis of 1,350 primary sarcomata (mostly in adults) gives the following results:

I. General Statement.

Locality.	Total.	Males.	Females.
Bones	385	217	168
Connective tissue	340	186	154
Other parts	341	141	200
Unclassified	284	158	126
Totals	1,350	702	648

II.—Detailed Statement Showing the Primary Seats of Sarcomata in Adults.

Bones Affected.				Connective Tissue.				Other Parts.			
	Total.	Males.	Fe-males.		Total.	Males.	Fe-males.		Total.	Males.	Fe-males.
Superior maxilla	102	53	49	Face	20	12	8	Breast	95	3	92
Inferior maxilla	48	31	17	Neck	20	12	8	Genital glands	64	40	24
Femur	61	34	27	Thigh	18	7	11	Eye	40	20	20
Humerus	22	13	9	Leg	13	6	7	Parotid	32	15	17
Tibia	19	13	6	Orbit	12	8	4	Skin	17	7	10
Innominate	19	12	7	Mediastinum	11	7	4	Palate	12	4	8
Skull	19	12	7	Peritoneum	11	8	3	Lymph glands	12	10	2
Scapula	12	7	5	Multiple	10	5	5	Kidney	8	3	5
Fibula	11	6	5	Nose	10	10	..	Rectum	7	5	2
Foot	6	5	1	Groin	8	7	1	Bladder	6	5	1
Ribs	6	5	1	Retroperitoneal	8	3	5	Tonsil	5	5	..
Sacrum	4	3	1	Arm	7	5	2	Submaxillary glands	4	4	..
Ulna	3	2	1	Shoulder	7	5	2	Lung	3	3	..
Radius	3	..	3	Scalp	6	4	2	Prostate	2	2	..
Clavicle	2	1	1	Abdominal wall	6	3	3	Larynx	2	2	..
Hand	2	..	2	Forearm	5	2	3	Pharynx	2	..	2
Coccyx	2	..	2	Hand	4	4	..	Vagina	2	..	2
Sternum	1	..	1	Popliteal space	4	2	2	Uterus	2	..	2
Unclassified	43	20	23	Upper lip	4	2	2	External ear	1	1	..
				Pelvis	3	..	3	Optic nerve	1	..	1
				Perirenal	2	1	1	Vulva	1	..	1
				Muscle	2	2	..	Colon	1	1	..
				Eyelid	2	..	2	Thyroid	1	..	1
				Foot	1	1	..	Mouth	1	1	..
				Infraclavicular	1	..	1	Suprarenal body	1	1	..
				Scapular	1	1	..	Spinal meninges	1	..	1
				Back	1	..	1	Tongue	1	1	..
				Axilla	1	..	1	Brain	1	1	..
				Gluteal	1	1	..	Unclassified	16	7	9
				Ischiorectal	1	..	1				
				Unclassified	140	68	72				
Totals	385	217	168	Totals	340	186	154	Totals	341	141	200

Gurlt's analysis of 741 sarcomata gives analogous results: 194 arose from the maxillæ (superior 96, inferior 83), 150 from the female breast, 45 from the testis, 33 from the parotid, 30 from the face, 30 from the thigh, 30 from the leg, 26 from the neck and submaxillary region, 20 from the inguinal region, 18 from the orbit, 18 from the arm, 18 from the foot, 15 from the nares, 13 from the eye, 7 from the ovary, etc. It is interesting to note the extreme rarity of the disease in some situations, such as the muscles, tendons, spleen, heart, great blood-vessels, etc.

Of 18 melanomata tabulated by Gurlt, 5 originated from the face, 3 from the leg, and 1 each from the parotid region, eye, rectum, liver, ovary, breast, abdominal wall, hand, thigh, and 1 was multiple. Of 128 cutaneous melanomata analyzed by Dieterich, 48 arose from the extremities, 41 from the trunk, 28 from the head, and 11 from the neck.

Of 50 myxomata in my list the seats of the disease were as follows:

Locality.	Total.	Males.	Females.
Thigh	8	6	2
Parotid	4	3	1
Breast	4	2	2
Perirenal	2	1	1
Popliteal	1	1	..
Pectoral	1	..	1
Loin	1	1	..
Arm	1	..	1
Testis	1	1	..
Soft Palate	1	...	1
Nasopharyngeal	1	1	..
Pelvis	1	..	1
Neck	1	1	..
Finger	1	1	..
Nose	1	..	1
Unclassified	21	7	14
Total	50	25	25

Pure myxomata—that is to say, tumors consisting of clear, glassy, translucent substance, like that of the jellyfish, certainly are very rare. I have met with only two or three cases of this kind. Myxomata are usually complicated by the presence of sarcomatous, fibrillar, chondromatous, or fatty elements that spoil their clear, glassy properties.

In one of the cases to which I have referred the patient was a man, aged twenty-six, with a circumscribed lobulated recurrent tumor growing from the subcutaneous tissue of the right loin. It was of four months' growth and the size of a large orange. Two and a half years before a similar tumor, the size of a man's head, had been removed from the same locality. At the operation for its removal the tumor was seen to be distinctly encapsuled and consisting of clear, transparent, vitreous, gelatinous substance. On microscopical examination it was found to consist of a homogeneous myxomatous matrix containing a few scattered small round cells. No stellate cells were noticed.

THE SARCOMATA OF INFANCY AND EARLY LIFE.

Not much more than a quarter of a century ago Virchow wrote, "Hardly any cases of congenital sarcoma are known." Since then vast additions have been made to our knowledge of the malignant neoplasms of early life, and scores of cases of congenital sarcoma have been reported. Unfortunately, most of these precious acquisitions are still buried in the archives of learned societies, where they are beyond the ken of practitioners. Even in treatises dealing especially with the diseases of children, little or nothing is to be found on this subject. In the course of the present article I propose to refer briefly to some of the chief advances in this direction, hoping, by so much, to make good some of the present deficiency. As I have shown in the article on "Cancer," that disease is practically unknown before puberty; consequently we may regard all the malignant tumors of early life as being of a sarcomatous nature.

Thus, of 56 consecutive cases under my observation, 14 originated in the first quinquenniad, viz., in the eye 7, kidney 2, testis, inferior maxilla, base of the skull, sacrococcyx, and tibia, each 1; 6 originated in the second quinquenniad, viz., in the liver, parotid, kidney, tibia, cervical lymph gland, and inferior turbinated bone, each 1; the third quinquenniad furnished 16 cases, viz., in the inferior maxilla 4, femur 3, fibula 3, tibia, humerus, acromion process, parotid, thigh muscles, external ear, and retina, each 1; in the fourth quinquenniad 20 cases arose, viz., in the femur 4, superior maxilla 3, inferior maxilla 3, lymph glands 2, testis, pharynx, kidney, parotid, base of the skull, humerus, orbit, and subcutaneous connective tissue of the back, each 1.

I have been greatly impressed with the large proportion of the neoplasms of early life that obviously arise in connection with embryonic developmental anomalies, to which I shall presently have occasion to refer more in detail. This gives the whole group a certain peculiarity; but it seems to me undesirable, on this account, to make a special morbid entity of these neoplasms as Birch-Hirschfeld and others have proposed. I think, however, it must be admitted that such tumors progress more rapidly, disseminate more frequently, and after removal recur with greater rapidity than their congeners of adult life. In this connection it is interesting to recall Volkmann's conclusion that of the sarcomata of adults, those arising from congenital blemishes (verrucæ molles, nævi materni, moles, etc.) were more malignant than others. In addition to being congenital, many tumors of this kind are also multiple *ab initio* and not infrequently they are bilateral.

I have found that the proportion of cases in which a history of heredity is recorded is considerably smaller than in the corresponding neoplasms of adult life; consequently I cannot corroborate Hutchinson's dictum that "malignant disease in young persons is generally inherited." The newly-born infants of mothers themselves the subjects of malignant disease are hardly ever thus affected. However, a few very remarkable instances of heredity have been recorded; for instance, Strümpell has reported a case in which two brothers died in early infancy with sarcoma of the left kidney, probably of congenital origin.

The Kidney.

Judging from the very large number of recorded cases, the kidney is one of those organs whence the malignant neoplasms of early life most frequently arise. The disease is probably of even more frequent occurrence in the kidney than in the eye, which most authors have placed before it. This proclivity of infants to malignant renal disease is the more remarkable when the great rarity of the affection at other periods of life is borne in mind. Thus, of 8,378 primary malignant neoplasms in adults my list shows that only 32 were of the kidney (24 cancers and 8 sarcomas). There are good reasons for believing that this great proneness of the kidney to originate malignant tumors in early life is intimately associated with a tendency to developmental irregularities, to which this organ is extraordinarily prone. It accords with this that renal sarcomata are frequently congenital, multiple *ab initio*, and bilateral; when of small size, it can be seen that such tumors are distinctly circumscribed, and that they usually indent the contiguous renal substance, rather than infiltrate it. In short, they appear to arise from elements detached from their normal connections during the course of development, rather than directly from the renal parenchyma. Many peculiarities in their histological structure tend to confirm this view. Thus they frequently contain striped muscle elements, which can easily be accounted for as sequestrations, when we recollect the close relationship normally existing between the rudimentary kidney and the contiguous muscle matrix. Tumors of this kind have been found in connection with the hilum of the kidney. I have observed with surprise the extreme rarity with which cartilaginous and osseous elements are found in these tumors. I know of only one instance of this kind, a case of congenital chondro-myxo-sarcoma reported by Heisholt. From this it may be inferred that the renal rudiments are much more closely associated with the lateral parts of the mesoblast than with the adjacent protovertebral mass. Moreover, since dermoid elements are never, so far as I know, found in these tumors, it may be inferred that the renal rudiments are as little related to the epiblast as they are to the protovertebral mass. Thus pathology may throw some light on the problems of embryology.

Epithelial elements of simple tubular or papillary cystic type are also found in the sarcomatous matrix; and it has been remarked, when they are present, that the myomatous elements are absent, and *vice versa*. It seems to follow from this that the tumors in which epithelial structures abound have a different origin from those which contain myomatous elements. Such cases have, on this account, often been described as "cancers."

There is much to be said in favor of the belief that many of these adenosarcomata arise in connection with "rests" of the Wolffian body. The papillary cystic formations met with are certainly highly suggestive of rudimentary glomeruli, such as abound in the Wolffian bodies. At the same time it seems to me probable that tumors of this kind may arise from congenitally separated portions of the renal parenchyma itself. In this connection it should be borne in mind that the number of lobules composing the human kidney is greater than is generally believed. According to Maresch, from eight to eighteen distinct lobules can easily be recognized in the fœtal organ, while many incomplete lobules also exist; so that altogether traces of from twenty to fifty lobules may be found in every fœtal kidney. These are sometimes very imperfectly integrated. Detached renal lobules of this kind may originate some of the sarcomatous tumors found growing from the renal pelvis, etc. Ricker's observations certainly lend support to these views. Hildebrand has reported an instance of sarcomatous disease arising in connection with abnormal union of the cortical and medullary parts of the organ.

Teratomatous tumors are not common in the kidney; but in a case reported by Hausemann an adeno-myxo-sarcoma appears to have originated in connection with a tumor of this kind.

It seems probable, from the observations of Grawitz, Lubersch, and others, that the tubular form of adenosarcoma often arises from suprarenal sequestrations included in the kidney or in its vicinity. These organs are closely associated in their development; and it is not uncommon to find their contiguous surfaces more or less fused together. Sequestrated bits of suprarenal tissue have often been demonstrated in the renal substance, as well as in connection with the capsule, etc. Many renal sarcomata and other tumors have now been described containing structures the counterparts of these; so that this origin for certain renal tumors may be considered as firmly established as any fact in renal neoplastic pathogeny. In a case of this kind lately reported by Eurich there was congenital absence of the corresponding adrenal; that is to say, it probably never had been separated from the kidney.

Sudeck thinks that some renal sarcomata arise from "rests" of hepatic origin; and certainly the histological structures shown in some of McWeeney's sections are very liver-like. The subject is still *sub judice*. The development of the kidney is of such a complicated nature, and so many adjacent structures are liable to be implicated, that it would be surprising if fragments of some of them were not frequently included in it. To such sources we must look for the germs whence most renal sarcomata arise.

In these tumors round cells and spindle cells predominate. They are well supplied with blood-vessels, and in some cases the telangiectasic development is very remarkable. Such growths are often described as endotheliomata, angiosarcomata, etc. Many tumors consist only of sarcomatous elements with more or less fibrillation, and myxomatous changes are sometimes met with.

Renal sarcomata generally present as large, more or less circumscribed, bossy, rounded masses, which often attain extraordinary size, especially when compared with the diminutive bodies of the infants who bear them. Instances have been reported of tumors weighing upwards of thirty pounds. They may contain cystic cavities—often of considerable size—with intracystic growths. Sections display a yellowish-whitish color, mottled here and there with areas of ecchymosis. They are of softish consistence. In nearly half the cases the disease is bilateral. Most cases are met with in early infancy; of Walker's 138 renal sarcomata of early life, no less than 114 of the patients were under five years of age. Boys are more prone to be affected than girls. The disease is seldom hereditary, for of Walker's 145 cases there was a family history of malignant disease in only 8.

Renal sarcomata progress rapidly, the average duration of life in the infantile form of the disease being very little over eight months. Death ensues from asthenia, when not due to interference by the tumor with adjacent organs, or to metastases. Neighboring parts are soon invaded; but the lymph glands commonly escape. As in other malignant intraabdominal tumors the glands in the lower part of the neck, just above the clavicle, may become enlarged in the course of the disease (Troisier's symptom). It is especially through the blood-vessels that the disease disseminates. Of forty-one cases Windle found secondary growth in seventeen, the parts affected being the liver, retroperitoneal glands, mesenteric glands, heart, diaphragm, adrenals, spleen, lungs, pancreas, intestine, pleura, renal vein, orbit, and elbow, in the order of frequency as named. Recurrence after operation is of great frequency, owing to the difficulty in completely extirpating the disease, and the half-hearted manner in which operations of this kind are usually undertaken.

I have seen malignant disease connected with the kidney of a male child, two years old, quite different from any of the foregoing. Laparotomy was performed for a large tumor occupying the left renal region; but the adjacent glands, etc., were so extensively infiltrated that its removal was not attempted. The child died not long afterwards; and at the necropsy the left kidney was found to be surrounded by a mass of soft, ecchymosed myxosarcomatous new growth, which had evidently sprung from the perirenal fatty envelope, for it was distinctly outside the renal capsule, and the kidney itself was unaffected. I have since seen a similar case in an adult; and the glands being unaffected, the disease was successfully removed together with the kidney. Tillmanns has reported a similar case in a woman, aged twenty-eight, in whom the growth was successfully removed; but recurrence subsequently took place.

The Adrenals.

It is convenient to consider adrenal sarcomata in this place rather than elsewhere, because of the close association of this structure with the kidney. It is very rare for any kind of neoplasm to originate from the adrenals. Of 13,824 primary tumors of all kinds—mostly in adults—consecutively under treatment at several large London hospitals (including 8,378 malignant neoplasms) I found only one instance of suprarenal tumor, an adenosarcoma. Gurlt's analysis of 13,971 neoplasms from the record of the Vienna hospitals does not include a single instance. From various sources I have collected records of thirty-six adrenal neoplasms, and of these rather more than one-third belong to the periods of infancy and childhood. The latter are invariably sarcomatous, although often described as cancerous, on account of the presence of epithelial elements. They are occasionally met with at birth; and they may be bilateral. Ricker believes that some tumors of this kind originate from renal sequestrations included in the adrenals. Accessory adrenal structures are of common occurrence in the kidneys and in their vicinity; and as above mentioned many so-called renal sarcomata originate in connection with them. Ribbert believes that he has traced a sarcomatous tumor connected with the outside of the capsule of the kidney in the vicinity of the pelvis to such a source. Marchand has found accessory adrenal structures in situations far removed from their normal habitat, such as the broad ligament and the epididymis, and certain tumors of these parts have been described as arising in connection with them. Hepatic "rests" as a source of adrenal tumors have also to be borne in mind.

Instances of adrenal sarcomata have been reported by Parker and Dalton in infants only a few weeks old, by Martin at five months, by Cohn at nine months, by Eberth at fifteen months, by Fox and Mankiewicz at two years, by Earle and Pitman at three years, by Lazarus at four years, by Greenhow at twelve years, by Peacock, Davies, and Fraenkel at eighteen years.

Peculiar constitutional disturbances are sometimes associated with these tumors. Thus in Pitman's case a large sarcoma of the left adrenal in a female child three years old was associated with general melasma, hypertrichosis, and external genitalia like those of an adult. In Fox's case, a female child two years old had a sarcomatous tumor, the size of a cocoanut, of the left adrenal which rested on and flattened the adjacent healthy kidney. It was of one year's growth. There were secondary tumors in the mesenteric glands and in the left lung. The child was of distinctly cretinoid aspect and disposition, being also very fat. There was peculiar lividity about the cheeks. The body was remarkably hairy, especially about the genital and pelvic regions. The vulva, labia, and clitoris were developed to a remarkable extent.

Adrenal sarcomata progress with great rapidity and are of a high degree of malignancy. In Cohn's case a round-celled sarcoma of the right adrenal disseminated in the liver, ovaries, kidneys, skull, and ribs. The child died six weeks after the disease was first noticed. In most of the above-mentioned cases metastases were met with, the lungs and liver being the organs chiefly affected.

In a case of Chaffey, a female child three years old, who had been ill for eight months and paraplegic for the last three, was found after death to have a round-celled sarcoma—of central origin—affecting the left adrenal. There were secondary nodules in the renal cortex and in the right ovary, and the adjacent lymph glands were enlarged. There were also numerous secondary growths in the skull bones, iliac bones, at the base of the sacrum, in the prevertebral region, and in the ribs. Many of these were symmetrical. In the lumbar region the spinal cord was compressed by an extension of the growth through the intervertebral foramina.

The Eye.

Most statistics show the very great frequency of malignant neoplasms in the eye during early life. These tumors are generally of intraocular origin, the great majority of them being retinal gliomata; but sarcomata of the uveal tract—both pigmental and non-pigmental—are now and then met with. Of one hundred and fifty-five malignant intraocular neoplasms at the Prague clinic, twenty-four were in children from one to ten years old. Retinal gliomata are peculiar to early infancy; they are rare after the age of five; and after puberty they hardly ever occur. They may be met with at birth; and exceptionally both eyes are simultaneously affected, but it is much commoner for the disease to begin in one eye and thence to spread to the other. Of eight cases within my own experience, in four the disease was almost certainly of congenital origin. There are good reasons for believing, as Wintersteiner and others have pointed out, that most of these tumors arise in connection with developmental irregularities affecting the evolving retina during embryonic life. According to Virchow, it is from the connective-tissue elements of the retina (neuroglia) that these tumors arise; but several modern observers (Greef, Hertel) have demonstrated the presence of ganglion nerve cells in retinal gliomata. These tumors are of rapid growth, very prone to disseminate locally and to recur after removal; but they rarely cause metastases. Sooner or later the second eye is generally affected, and the disease spreads within the cranium. As soon as the globe of the eye is destroyed, the growth increases with great rapidity, projecting from the orbit as a reddish fungoid mass. Such tumors are soft and vascular, consisting mainly of small round cells.

Their features are well illustrated by the following case, which I had the opportunity of observing.

The patient was a little girl, who when one year old came under Lawson's care for glioma of the left eye, which was enucleated. The eyeball was distended by the growth. Six weeks later the right eye was removed for similar disease, which caused blindness and great pain. A few weeks after the last operation recurrent growth was noticed in the left orbit. As no further operation was done this increased with great rapidity, forming a huge, reddish, bossy, fungoid outgrowth, which protruded from the orbit and covered the whole of this side of her face. The child became very weak and emaciated; and died thus of asthenia about four months after the last operation. There was no return of the disease in the right orbit. During the last few days of her life she had several epileptiform convulsions, but no other brain symptoms. At the necropsy the left orbit and adjacent parts were found to be infiltrated by cerebriform growth, a large mass of which projected into the cranial cavity, in the vicinity of the pituitary fossa, compressing the crura cerebri. Numerous secondary growths were disseminated throughout the dura mater. A large mass of similar cerebriform growth was found in the right deltoid muscle. The nasal and buccal cavities were not invaded. There were no other noteworthy changes.

The occurrence of congenital melanomata of the iris has been reported by Graefe; and Virchow has described a sarcomatous tumor of the iris of a male infant, in which many myeloid cells were found. The tumor recurred after removal, but was afterwards cured by thorough extirpation.

McKay has met with congenital sarcoma of the choroid, Steffen with fibrosarcoma at fifteen months, and in a girl fourteen years old Williamson found spindle-celled leucosarcoma of the iris. The intraocular tumors of early life are seldom hereditary; but a few remarkable exceptions to this rule have been recorded. Thus Lerche observed the disease in four out of a family of seven children; and Sichel knew of four children of one mother who were all affected.

A considerable number of malignant neoplasms arise in the orbit during early life, quite independently of the eyeball. It is probable that most of these originate in connection with "rests" derived from the evolving eye or orbit. Thus we must look to ocular "rests" for the germs whence orbital melanomata arise, as in cases reported by Lebert, Curling, and others, and to retinal "rests" may be ascribed certain orbital gliosarcomata to which Virchow has called attention. Lagrange has met with myxosarcoma of the optic nerve in a boy five years old. Other examples of rapidly growing orbital sarcomata have been reported by Knaggs in a child two years and nine months old, by Lambert in a boy of three, and by Snell in a girl of four. Besides such tumors as the foregoing, a certain number of orbital malignant neoplasms appear to arise from germs resulting from developmental irregularities connected with the evolution of the orbit. The orbit is, in fact, a favorite seat for congenital tumors, nævi, cysts, etc. Teratoid formations are also apt to occur in this locality. Courant removed a large tumor of this kind from a newly born male child, which contained heterotopic elements representative of all the blastodermic layers; and there was defective development of the corresponding orbit. Baer and Weigert have reported a similar case. It seems likely that tumors of this kind originate as fœtal inclusions in the orbitofrontal fissure. In the following case a sarcomatous tumor seems to have arisen in this connection.

A young woman, aged 19 years, had left proptosis and other signs of orbital tumor. On examination a firm nodulated new growth was found attached to the upper margin of the orbit. The adjacent lymph glands were normal. Excision of the tumor was performed, and the growth seemed to be limited to the upper part of the orbit and was unconnected with the eye. Recurrence *in situ* took place two and a half years later and excision was again resorted to. A further recurrence took place nine months later, for which the orbit was cleared out. The globe and optic nerve were quite free from disease. The tumor was a sarcoma that seemed to have originated from the upper and outer part of the orbit. It contained no gland elements.

As demonstrated by Axenfeld, islets of cartilage are of common occurrence in the normal orbit. These are no doubt "rests" derived from the skeletal matrix of the evolving orbit. Dermoidal elements, similarly derived from cutaneous sequestra, are also common. To such sources we may ascribe the origin of the "ossifying epithelioma" of the orbit, described by Silcock, in a young boy; as well as the various more or less malignant ossifying and chondrifying orbital tumors, of which examples have been recorded by Reid, Beaumont, and others.

Other sarcomatous tumors are found in the orbit which originate quite outside it. Most of these spring from the region of the basisphenoid where they appear to arise in connection with developmental aberrations in the vicinity of the anterior extremity of the notochord, hypophysis, etc.

Some remarkable cases of this kind have been published by Targett in a male infant one year old, by Moore in a boy aged one and a half years, by Jessett in a female child one year and seven months old, by Pollock in a girl of five, by Dickinson in a boy of twelve, etc.

The following illustrative case is by Lawson:

The patient was a male child only two days old, in whom the disease existed at birth; there was rapid recurrence after removal of the tumor, which was a multilocular cyst with much solid new growth On histological examination it proved to be a round and spindle-celled sarcomatous teratoid new formation containing cartilage, epithelial elements, and other heterotopic structures.

Holmes has met with a similar case. Many instances of the development of malignant tumors in early life from the external surface of the eye have also been recorded, in which the disease has been shown to have originated from congenital blemishes there, such as dermoid patches, warts, melanomata, etc. These are derived from "rests" of the primitive skin that covers the eye in early embryonic life. As the eyelids evolve this skin is gradually converted into conjunctiva. The last part to be converted is the horizontal meridian. Where the covering remains imperfect from a slight degree of coloboma or otherwise—which usually is at the outer and lower portion of the corneoscleral margin—these congenital blemishes are most apt to occur. It is just in these localities that most of the malignant neoplasms now under consideration also arise. Instances of melanosarcomata thus originating have been reported by Virchow. Other malignant tumors thus arising have been described by Dujardin in an infant twenty months old, by Panas in children twelve and thirteen years old, by Rogman in a boy of fourteen, etc.

The Bones.

Superior and Inferior Maxillæ.—Many cases of malignant disease arise in connection with these bones during early life, most of them being myeloid sarcomata. Of 29 cases collected by me, 8 originated from the superior maxilla and 21 from the inferior. Of the former group 3 were congenital, 1 occurred in an infant 3½ years old, 2 between the ages of 10 and 15, and 2 between 15 and 20 years. Of the latter group 4 were congenital, 3 occurred in the first year, 1 at 2¾ years, 4 between the ages of 5 and 10 years, 5 between 10 and 15 years, and 4 between 15 and 20 years. This list includes 4 odontomas, 1 in a girl 2¾ years old, 1 in a boy of 10 years, and the other 2 in women 18 years old. It also comprised 2 congenital enamel-organ tumors (Massin and Verneuil), 4 cases of round-celled sarcoma, 1 of round and spindle-celled sarcoma, and 1 of congenital myxoma.

Heath has recorded a case of symmetrical myeloid tumor. The patient was a boy seven and a half years old with a large, elastic tumor on each side of the inferior maxilla, in the vicinity of the molar teeth. A swelling was first noticed on one side, when he was only one and a half years old, and afterwards on the other. On coming under observation the child was in good health, but he had formerly suffered from rickets, and his legs were somewhat deformed thereby. He had cut his first permanent molar, but the temporary molars were still present. Both tumors were freely removed, and when the patient was last heard of some years later, he was free from any return of the disease. These tumors are preserved in the Museum of the Royal College of Surgeons; they probably originated from the periodontal membrane of the evolving second molar teeth.

Another remarkable instance of multiple myeloid sarcoma has been reported by Parkin. The patient was an infant three and a half years old. An elastic globular tumor firmly connected with the alveolar process of the right superior maxilla presented in the vicinity of the canine and molar teeth. In addition to this, the child also presented a large soft tumor, connected with the front part of the inferior maxilla, which projected backwards into the floor of the mouth and forward so as to cause the lip to protrude. The former tumor had been nine months in growing and the latter six months; and in their growth both had displaced the adjacent teeth. The whole of the front part of the inferior maxilla was excised with the tumor attached and five days later the right superior maxilla was completely excised together with the tumor. The tumors were alveolar sarcomata of central origin, consisting of numerous small round and spindle celled elements with many myeloid cells, and well-marked fibrillation. The inferior maxillary tumor had invaded the soft parts of the floor of the mouth. Three months after the last operation the child was well and free from recurrence.

Cranial Bones.—In early, as in later life, the cranial bones rarely originate malignant tumors. Most cranial sarcomata of early life spring from the vicinity of the basisphenoid, and I have previously referred to these. Other tumors of this kind arise from the bones of the cranial vault, from the temporal bones, etc. These are generally of periosteal origin, and round cells predominate. They are commonest in children under five years of age. Of fourteen skull sarcomata tabulated by Butlin, three were in young infants. After a time the disease disseminates in other cranial bones. In fact, so far as the spread of these tumors is concerned, the cranium may be regarded as a single bone; hence multiplicity is the rule rather than the exception. Both the intra- and extracranial aspects of the affected bones are usually invaded. In spite of this, marked brain symptoms are rare. The disease progresses rapidly, the average duration seldom exceeding eighteen months. Metastases are of common occurrence. Some of these intracranial periosteal sarcomata contain green coloring matter (*chloromata*); in other respects they are just like their non-colored congeners. This green coloring is reproduced in the secondary growths. Of fourteen chloromata tabulated by Lang, five were in children under ten years of age; and Aran has pointed out that children are especially prone to this form of disease. Birkett has met with myeloid sarcoma of the frontal bone in an infant only two months old.

Most temporal sarcomata arise from the periosteum of the tympanum, as in cases reported by Schwartze in a boy three and a half years old, by Barr in a boy twelve and a half years old, by Hang and Milligan in girls of eighteen. Several cases of round-celled tympanic sarcoma in young children have been recorded by Gruber. Tympanic sarcomata have a special tendency to spread within the cranium. They are as malignant as other periosteal sarcomata; but they appear to have no special proclivity to invade other cranial bones. Bryant has published an account of a periosteal sarcoma of the temporal bone in which the disease appeared to have originated in connection with the mastoid; the patient was a girl ten and a half years old. In this case also the disease spread within the skull.

Long Bones.—The long bones rarely originate malignant tumors until the third quinquenniad, when a large number of cases arise. Of Gross' 147 cases, only 3 arose during the first quinquenniad, and 3 during the second; whereas 45 cases originated between the ages of 10 and 20 years. Similarly of 119 cases tabulated by Butlin and Colby, 3 belong to the first quinquenniad and 3 to the second, whereas 35 originated between the ages of 10 and 20. The femur, tibia, humerus, and fibula are the bones most frequently affected, in the order stated. More than half the total number of cases arises from the femur. Of eleven early-life sarcomata of the femur tabulated by me, the youngest occurred in a boy nine years old, five belonged to the third quinquenniad, and five to the fourth. The lower end of the bone is the usual starting-point of the disease, which is generally of periosteal origin. Jacobi has cited an instance of congenital sarcoma of the femur, and Billroth one of the tibia. Butlin reports instances at one and a quarter and two and three-quarter years. Lockwood has met with round-celled sarcoma of the radius in a female infant eleven months old. At these early ages the disease generally appears to be unusually malignant.

Scapula.—The scapula is remarkable among the skeletal bones for the early age at which it originates malignant tumors; and it is noteworthy that these early occurring sarcomata are exceptionally malignant. Of twenty-five bone sarcomata in infants, collected by Poinsot, in eleven the scapula was the part affected. Instances have been published by Jacobi (congenital), Targett (rhabdomyosarcoma, at the age of six months), Morgan (infant), Ball (in a boy two and a quarter years old), and Cabot (in a boy of twelve).

The Muscles.

Transversely striped muscle elements are frequently associated with the malignant tumors of early life; but, strange to relate, tumors having this structure never arise from the muscle elements themselves. These, the most important of all the tissues of the body, since they comprise nearly half its weight, are one of the few structures almost immune to tumor formation. The explanation of this immunity is one of the riddles of neoplastic pathogeny yet to be solved. Curiously enough, this immunity extends also to the connective-tissue elements that help to form the muscles, although it is not so complete for them as for the muscle elements themselves. It is, however, indubitable that the connective-tissue elements of muscles are very much less prone to originate neoplasms than the connective tissue of the organism in general. Tumors of this kind are as rare in early life as at later periods. Of thirty malignant muscle tumors tabulated by Guitton, four originated in early life, at from five to thirteen and a half years. Marshall has reported a case of spindle-celled sarcoma in the calf muscles of an infant five months old that was probably congenital. Broca met with sarcoma of the sheath of the peroneal muscles in a boy of six; Bérard with sarcoma of the pectoralis major in a girl of twelve, and Barling with alveolar sarcoma of the triceps in a young woman of twenty.

The Skin.

The skin is a favorite seat of congenital neoplasms, many of which are malignant. Of 1,063 "histologically verified" malignant skin neoplasms tabulated by Gallard, 6 were in children under ten years old; Picot's analysis of 424 malignant neoplasms of early life ascribes only 8 to the skin. These data seem to me to underestimate the liability. At any rate, there are on record a large number of cases of malignant cutaneous neoplasms in infancy, and even at birth. Among the commonest congenital blemishes of the skin, moles, nævi, and verrucæ molles may be mentioned. Malignant neoplasms often start from these, but not so frequently in early as in later life. Tumors thus arising may be pigmented or non-pigmented; and though they are often described as "cancers," on account of the presence of epithelial elements, they are invariably sarcomatous. Instances of congenital melanosarcoma have been reported by Variot; Denzler, in a male infant eight months old, met with melanosarcoma of the back of the hand, of which the child died two months later with metastases in the lungs; Gussenbauer has reported melanosarcoma of the skin of the cheek in a girl eight years old; several of Pemberton's cutaneous melanoses were in children under ten years of age; and in a girl of twelve, Wardrop saw a malignant melanotic tumor that had grown from a congenital pigmented wart of the skin of the abdomen. Similar tumors sometimes arise in the subcutaneous tissue, as if from epidermic "rests" embedded there. Of non-pigmented sarcomata thus arising, congenital cases have been reported by Neuhaus, Karewski, Holmes, and others.

In Neuhaus' case the patient was a child, two months old, with recurrent sarcoma of the skin of the left leg. There were numerous secondary growths in the skin and subcutaneous tissue of the trunk, lower extremities, etc. Excised nodules showed the structure of round-celled sarcoma. The child died soon afterwards; and at the necropsy numerous metastases were found in many parts of the body. The history of the disease was as follows: Five days after birth a tumor connected with the skin of the left leg was noticed, which, having increased to the size of a hen's egg, was excised when she was five weeks old. Shortly afterwards there was local recurrence; a tumor soon appeared beneath the skin over the right clavicle, and the inguinal and cervical lymph glands became enlarged.

In a case by Holmes, the patient was a boy, fourteen days old, with a rapidly increasing fibrosarcomatous cutaneous tumor, reaching from the ear to the shoulder; and just above it, there was a large nævus. Senftleben has described the case of a boy, three weeks old, in whom a congenital nævus of the thigh, which was injured some weeks after birth, became the seat of a sarcomatous tumor, which recurred after removal. In a male infant, three months old, with a cutaneous nævus of the back, Cramer reports the development of sarcoma after an attack of smallpox. In a newly-born child Ritter met with what he calls "a congenital cancerous polypus" of the tip of the nose; there were enlarged lymph glands in the submaxillary and parotid regions, which increased and contributed to death by asphyxia three weeks later. There were also metastases. Although Ritter calls the "tumor" cancer, his own description of its structure is much more like that of sarcoma. It is probable that in this case the malignant disease supervened in connection with a congenital polypoid outgrowth, such as Lannelongue has described as occurring in this situation.

Jolly has reported an example of sarcomatous angioma at the root of the nose in a male infant seven months old. Selberg has described "cancroid" of the skin of the scapular region in an infant of six months, which was first noticed four weeks post partum. The disease presented as an eroded, knobby, walnut-sized tumor. Microscopical examination revealed in-growing interpapillary processes and "nests"; and this was thought to justify the diagnosis of cancer, although none of the clinical signs of this disease was present. In a child three and one-half years old, Lukasiewicz has met with a similar tumor.

Several instances of cutaneous malignant disease in early life have been reported in connection with xeroderma pigmentosum, etc. On considering Kaposi's account of the "sarcocarcinomatous nodes," which he observed on the faces of girls, aged ten and seven years, who had suffered from earliest infancy with a severe form of xeroderma, it seems to me that the facts there described are, on the whole, more consistent with sarcoma than epithelioma, with which this distinguished dermatologist has classed them. In like manner we may regard the very similar cases of cutaneous malignant disease of the face in two brothers, aged eleven and twelve, the subjects of xeroderma pigmentosum, as recorded by Esmarch; as well as the analogous instances by Rüder, in which several children of a family were affected.

A congenital sarcomatous tumor of the right side of the face has been described by Charbon; and Davies-Colley has removed a polycystic fibrosarcomatous tumor from beneath the skin of the back of a youth, sixteen years old, which appeared to have started from a congenital lymphangioma.

In a girl of fourteen, Braun has seen "cancer" develop in the scar of a burn of the scalp, the disease proving fatal by perforating the cranium. Curtis, in a child eight years old, has met with a similar condition. Sangster has reported malignant disease of the scalp in a youth of sixteen. In a young woman Conner met with sarcoma of the same part; and in a youth of nineteen Frerichs has described "cancer."

Janisch has seen "hæmangioëndothelioma tuberosum multiplex" in a girl of seventeen, in whom the disease began in the skin over the sternum, at the age of seven years.

Bryant, Volkmann, and others have reported cases of congenital keloid. Vidal has witnessed the same disease in a vaccination scar, in an infant three and one-half months old. Nasse, in a boy aged eleven years, met with multiple keloid with contraction, the disease being of four and one-half years' duration.

The Brain.

In early life many malignant tumors arise from the brain and its membranes. Of 34 primary malignant intracranial tumors tabulated by the London Pathological Society's committee 9 were in patients under twenty years of age, 1 being under the age of five. Of 17 early-life sarcomata analyzed by Mariage 8 were cerebellar, 6 cerebral, 2 pituitary, and 1 arose in the fourth ventricle.

Most of these malignant brain tumors are gliomata. Unlike their retinal congeners brain gliomata seldom arise during early infancy; so far as I know, the disease has never yet been met with at birth; and during the first quinquenniad such tumors are rare. Of 28 early-life cases tabulated by me the age distribution was as follows: First quinquenniad, 4 cases; second quinquenniad, 13 cases; third quinquenniad, 6 cases; fourth quinquenniad, 5 cases. Gliomata are commonest in the cerebellum, the cerebral cortex, the pons, the basal ganglia, etc. The pathogenesis of these tumors is now being much discussed. Virchow traced them to the neuroglia, which he believed to be of parablastic origin; His, Cajal, and others, now maintain that the neuroglia is an epiblastic derivative. Klebs finds that nerve cells, as well as neuroglia elements, are constituents of all gliomata; and that they form a large part of many of these tumors. Greef, Hertel, and others confirm these observations. To show how highly organized the nerve constituents of some of the firmer kinds of glioma are, it may be mentioned that Klebs succeeded in transmitting central excitations, through them, to peripheral motor nerves. Tumors of this kind appear to differ little from overgrown local malformations. They progress slowly, and seldom manifest malignant properties.

Most gliomata of early life are, however, much less highly organized than the foregoing. They consist almost entirely of cells, resembling those met with during early stages of the development of the brain. Their nuclei are large, and their surrounding protoplasm is so ill defined that the nuclei appear to be embedded in a common protoplasmic matrix. According to Golgi these cells are united by radiating fibres ("spider cells"). Large-sized, ganglionic cells are also met with. The margins of these soft gliomata are usually so ill defined that they present as local enlargements rather than as circumscribed tumors. As they are very rich in blood-vessels without walls, hemorrhages are common and often cause death. This form of the disease progresses rapidly, spreads to adjacent parts of the brain, and generally ends fatally in a comparatively short time—often in only a few months; but lymph-gland dissemination and metastases are very rarely met with. Peabody has reported sarcoma of the cerebellum in a child of three, whose mother had sarcoma.

Ströbe and Ziegler have met with appearances that point to some connection between these tumors and certain developmental irregularities; in fact, the general aspect of cerebral gliomata (which may be multiple *ab initio*) seems to indicate that they arise in connection with developmental defects, somewhat similar to those that determine multiple sarcomata of the cauda equina and peripheral nerves.

Examples of sarcomata of the pituitary body have been reported by Audry in a boy six years old, and by Mirinesen in a girl of eleven. Congenital tumors containing various heterotopic structures are met with in this locality, of which Hale White has reported a case in a boy of twelve, in which the tumor contained striped muscle, nerve fibres, and sympathetic ganglia. In a man, aged twenty-two, Bowlby has met with a somewhat similar tumor, which consisted of connective elements, epithelial cysts, bone, and blood-vessels. In a specimen described by Sainsbury, the bulk of the tumor consisted of fibro-sarcomatous tissue, lined externally by cutis vera. Rindfleisch has met with a remarkable tumor of this locality in a sixth-month fœtus. It consisted of two parts, one of which projected into the cranial cavity and the other into the mouth; these were united by a pedicle which perforated the basisphenoid at the pituitary fossa. The tumor was composed of embryonic connective tissue, in which were embedded cartilaginous, osseous, muscular, nervous, and glandular structures; and that part which projected into the cranium contained traces of a face and of limbs, and a fragment of intestine.

Coats has described a remarkably interesting case of sarcoma of the pineal body in a youth of thirteen; in addition to sarcomatous structures the tumor contained epithelial elements, smooth muscle fibres, cartilage, blood-vessels, and a little brain sand. Coats suggests that it may have arisen from residua of the pineal eye. Somewhat similar tumors have been met with by Turner, Weigert, Falksen, and others.

In a youth of nineteen, Ransom demonstrated a large oval-celled sarcoma of the corpora quadrigemina; and in a girl of fifteen, Westphal met with multiple sarcomata of the brain and meninges. As instances of pia-matral tumors may be mentioned Ashby's case of psammoma of the choroid plexus in a boy three and one-half years old; Beevor's case of cerebellar psammoma in a boy of eleven, and Eve's psammoma of the choroid plexus in a youth of nineteen. Examples of villous papilloma of the choroid have been reported by Allbutt in a girl nine years old; and by Douty in a youth of seventeen. Le Breton mentions sarcoma of the fourth ventricle in a boy of sixteen. An instance of small round-celled sarcoma of the pia mater of the fourth ventricle, in a girl of fifteen, has been reported by Turner; and in a girl of the same age, Lancereaux met with a large polypoid myxoma growing from the same structure, which caused coma and death.

Sarcomata and chloromata of the dura mater also occur in quite young children, and are exceedingly malignant.

The Tongue and Mouth.

Sarcoma of the tongue is a rare disease, of which only about two dozen cases have been recorded. Several of these originated in early life. Congenital cases have been reported by Jacobi and Mason. In Jacobi's case, a tumor the size of a hazelnut projected from the dorsum, where it was first noticed the day after birth; in the course of three months it attained the size of a walnut, when it was removed. When last heard of, five months after the operation, there was no recurrence. It was a round and spindle celled sarcoma, containing a small cyst and striped muscle. In Mason's cases several pedunculated, fibrocellular tumors were met with on the dorsum of the tongue. They remained quiescent until adult age, when they increased rapidly. In connection with such cases as the foregoing, it is well to bear in mind a curious congenital abnormality described by Hajek. From the base of the tongue, in front of the circumvallate papillæ, an outgrowth nearly an inch long projected, which was composed of structures like those of the tongue itself. Hence Hajek looked on it as a rudimentary accessory tongue. Hickman has met with a congenital tumor of the dorsum linguæ, in a newly born child, which contained racemose glandular structures. The tumor, which was the size of a small walnut, projected from the base of the organ in front of the epiglottis; and it caused the child's death by asphyxia a few hours after birth. Lang has seen a similar tumor in a girl of thirteen, which was of three years' duration.

Lang has also reported a case of "fibro-chondro-osteoma lipomatodes" in a woman of twenty-two; it presented as a hard, rounded tumor the size of a hazelnut, which projected from the dorsum of the tongue. It was first noticed when she was twelve years old, and it had since slowly increased. In a girl of fifteen, Weber saw a similar tumor, the size of a walnut, that had existed for upwards of eight years. Arnold and Bastien have described congenital tumors of similar structure. Congenital multiple lipomata and fibrolipomata have been reported by Poncet and Jacopo; and angiomata by Halen and others. Littlewood has recorded an example of round-celled sarcoma of the middle two-fourths of the tongue in a youth of seventeen; it formed a large tumor and caused enlargement of the glands beneath the jaw. The organ was extirpated and enlarged glands were removed; but the disease recurred in the glands and in the left tonsil. From a woman, aged twenty-four, Godlee removed an adenosarcomatous tumor which contained a calcifying nodule in its centre; and M'cWeeney met with fibromyxoma in a pugilist of twenty-three. Paget mentions having removed a "fibrocellular" tumor, of three years' growth, from the apex of a young man's tongue, in the substance of which it had grown.

From the top of the pharynx, chiefly from the vicinity of the basisphenoid, polypoid tumors not infrequently grow into the pharynx. They are commonest in young adults, but a good many cases occur in infancy and childhood. I have seen an instance in a youth, who first noticed the tumor when twelve years old; and in a girl of nineteen, this tumor being of adenosarcomatous nature. Margolin has reported a case at the age of two, Dumeil at five, and Massé several cases at from two to five. Wolfenden and Icart have each seen the disease in girls of fifteen, and Lloyd in a youth of seventeen. In these tumors, fibrous, myxomatous, or sarcomatous elements predominate, and sometimes there are glandular structures. From the same situation congenital skin-covered, piliferous tumors also arise, which besides fibrocellular elements and fat, contain also heterotopic structures, such as striped muscle and cartilage. These seem to arise in connection with developmental aberrations in the evolution of the pituitary body. It is probable that minor anomalies, arising at a later period, determine the formation of the glabrous pharyngeal polypi.

Berg, in an infant of four, has met with a malignant tumor of the soft palate, containing glandular elements. An account has been published by S. Paget of a sarcomatous tumor of the hard palate, which contained epithelial pearls, the patient being a woman of twenty-one.

A few cases have been described of primary sarcoma of the tonsils in youths of from seventeen to eighteen.

Stephan has reported an instance of sarcoma of the œsophagus in a child of five; the tumor extended from the level of the tracheal bifurcation to the cardia.

The Stomach.

In early life malignant disease of any part of the gastrointestinal tract is of great rarity. Of two thousand necropsies on children analyzed by Steiner and Neureutter, not a single instance of malignant disease of the stomach was met with. Congenital hypertrophy of the pylorus—not such a very rare condition, judging from the numerous cases lately recorded—has often been mistaken for congenital malignant disease, as in cases reported by Wilkinson and others.

Congenital adenomata are occasionally found in the gastrointestinal tract; in the stomach examples have been described by Hueter, Schmorl, and others. These growths are of an innocent nature; but occasionally they originate malignant disease. Kühn has described a case of this kind in a female infant two years old. A commoner occurrence is for inflamed tumors of this kind to be mistaken for malignant disease, as in Cullingworth's case. Here there was a polypoid tumor—evidently congenital—attached to the lower border of the pylorus, in an infant five weeks old. Histological examination revealed tubular structures, lined by cylindrical epithelium, as in cancer, but there were no clinical signs of malignancy. Pitt has met with lymphadenoma of the stomach in boys from four to twelve years old.

The Intestine.

Malignant disease of the intestine in early life is of more frequent occurrence than of the stomach, but it is not at all common. The instances of so-called "cancer" of the small intestine, reported by Duncan in an infant three and one-half years old, and by Spanton (ileum) at twelve, were evidently sarcomatous. Madelung has published fourteen cases of sarcoma of the small intestine in patients of various ages, mostly young. These growths are often multiple and sometimes congenital. Most of them arise from congenital adenomata. In an infant a few days old, Stern met with a polypoid angiosarcoma of the ileum, which had caused death by obstruction. In a boy of seven, Debrunner has also met with sarcoma of the small intestine. Pépin has described sarcoma of the jejunum in a girl five years old, and Bessel-Hagen a similar case in a boy of seven.

In the large intestine similar neoplasms have been met with, but they seem to be rarer. In a boy of five, Cathelin found multiple polypi scattered throughout the cæcum and colon; Pébroff has seen malignant disease supervene and in connection with changes of this kind. Debrunner reports sarcoma of the transverse colon in a boy of three; and Steiner's case of "alveolar cancer" of the sigmoid, in a child of nine, also belongs here. Kanthack met with "myxosarcoma" of the ascending colon in a lad of seventeen, which on second thought he fancied might be "colloid carcinoma." He would, I think, have done well to have kept to his first diagnosis; for, according to my experience, the so-called "colloid cancers" of early life are invariably myxomatodes.

In a girl of five, Homans found a small spindle-celled sarcoma of the cæcum. Laparotomy was performed, and a tumor growing from the anterior wall of the cæcum was discovered, which had invaded the ileo-cæcal valve, and was adherent to the ileum. It was successfully extirpated, together with the affected bowel. Abbe, in a youth of sixteen, met with sarcoma of the caput coli. A large tumor presented, which was excised with a part of the bowel. Adjacent lymph glands were infiltrated. The patient died thirty-six hours after the operation.

The Rectum.

The rectum is remarkable for the comparatively large number of cancers that arise from it in early life, and the earliest authenticated instance of cancer has been met with in the rectum, viz., Stern's case in a girl of eleven. Over a score of rectal cancers, in patients under twenty, might easily be collected.

A few instances only of rectal sarcoma have been recorded, some of them being melanotic, and in one instance ossifying changes were in progress. Hugenberger has met with a cartilage-containing tumor in Douglas' pouch. In early life rectal sarcomata are rare, but congenital adenomata are common. Guérsant has tabulated fifty cases of these polypi in children. Besides glandular elements they usually contain fibrous and myxomatous structures. Occasionally they undergo sarcomatous changes, but much less frequently than the somewhat similar vaginal growths. They have not been noticed to contain striped muscle elements. Probably few of these rectal polypi are the outcome of embryonic aberrations, connected with the development of the genitourinary passages; they should rather be regarded—like most other gastrointestinal adenomata—as malformations of the local mucosa; this may account for their comparatively innocent nature, when compared with the uterovaginal growths.

Hamon has reported the case of a man of twenty-five, the subject of rectal polypus since early infancy, in whom malignant disease supervened soon after excision of the tumor. In a siren monster, with imperforate anus, Ahlfeld found that a malignant tumor had developed in the blind end of the large intestine. Rectal sarcomata have also been reported as arising from leiomyomata; and similar instances have been met with in other parts of the gastrointestinal tract.

The Liver.

The number of cases of primary malignant disease of the liver that have been recorded as occurring in early life is very considerable. Such cases are much more numerous than I was aware of until I specially studied the subject; and many of them are of congenital origin. These tumors are often described as "cancer," but I think there can be no doubt that this is a mistake. Not infrequently there may be found in the liver circumscribed nodules of hepatic tissue quite detached from the rest of the organ. These may be regarded as portions of hepatic tissue that have become separated from their normal connections during the developmental period or subsequently. Such nodules are often designated "adenomata." Probably many of the malignant liver tumors of early life arise from these residua. Birch-Hirschfeld reports that of four hundred necropsies on newly born children, primary malignant disease of the liver was met with in two; and in both these cases the disease was diffuse. An example of hepatic myxosarcoma in a small, well-nourished girl eight years old has come under my notice, and I have seen an almost exactly similar case in a young adult. Other examples of this form of malignant disease have been reported by Meisenbach in an infant aged four months, and by Cornil in one of eight months. In some of the congenital cases the intraabdominal tumor has been so large that it has caused difficulty in delivery. Instances of so-called cancerous tumors of this nature have been recorded by Noeggerath, Kilian, and Wedl. In the two first-named cases the diseased liver weighed over two pounds, the weight of the infant without the tumor being under six pounds. De Ruyter has met with congenital lymphosarcoma in an infant ten days old, Parker at three weeks, Heaton at eight weeks, Lendruf at four months, and West at eight months. Pepper reports "cancer" in an infant eight weeks old, Gross "scirrhus cancer" in a male colored infant aged three months, Gee "alveolar sarcoma" at four months, Crouse "encephaloid cancer" at five months, Bahn "cancer" at six months, Ollivier "encephaloid cancer" at eighteen months, Weichselbaum "malignant adenoma" at twenty months, Henoch "medullary sarcoma" at two and a half years, Wolff "encephaloid cancer" at three years, Tooth "diffuse lymphosarcoma" at five years, Leichtenstern "cancer" at seven years, Kottmann "cancer" at nine years, Deschamps "encephaloid cancer" at eleven years, Pye-Smith and Birch-Hirschfeld "cancer" at twelve years, Roberts "medullary sarcoma" at twelve years, Lewis "encephaloid cancer" at thirteen years, and Henschen "telangiectasic cystic cancer" at fourteen years.

In a girl of eleven, König successfully excised an enormous multilocular cystic tumor of the liver that contained over three litres of fluid. The cysts were lined with cylindrical epithelium.

Israel extirpated a telangiectasic sarcoma, weighing 1,225 gm. ($2\frac{7}{10}$ lbs.), in the case of a girl of fifteen. She died one hundred and ten days later, with metastases in the right mamma, the lungs, liver, and dorsal spine.

The Spleen.

When we consider the great functional activity of the spleen, its abundant blood-supply, and the unusually large proportion of its cellular elements, we cannot help being surprised that it so very seldom originates any form of neoplasm, malignant or otherwise. This immunity extends also, to a certain extent, to secondary neoplasms; for although the spleen is just as much exposed as the liver to the incidence of malignant dissemination, yet it very much less frequently originates secondary new formations. It seems not unreasonable to suppose that this comparative immunity of the spleen is in some way connected with its functional activity, which enables it to destroy and make away with cells manifesting malignant properties, whether these are derived from its own constituents or those of other parts.

This leads me to recommend the trial of splenic extract as a remedy for malignant tumors.

I can cite the following examples of malignant splenic disease in early life. Collier in a child six years old found a peculiar tumor of this kind which Picou and Ramond think arose from pancreatic "rests," such as they have shown to exist in this organ in a three months' human embryo, and to which they ascribe the origin of a case of primary malignant disease of the spleen investigated by them. Gaucher had previously reported a similar case. To this category probably belongs the multilocular cystic tumor for which Thornton extirpated the spleen of a young woman, aged nineteen years. Notta's case of "cancer" of the spleen in a young infant may also be mentioned here. We must also remember that cysts may arise in the spleen from included sequestrations of the peritoneal epithelium, of which Ribbert has described an interesting case; and from "rests" of the intestinal mucosa.

Péan and Magdelain have met with a large cyst in the spleen that contained three litres of serous fluid; the patient was a woman of twenty, and symptoms of the tumor had been noticed for two years.

Cysts with blood-stained contents have been reported by Marcano and Féréol, Baccelli, and others. Langhans has described a case of cavernous angioma; Besnier one of myxo-fibro-chondroma; and Andral a congenital cyst, probably derived from a "rest" of the intestinal mucosa.

Pancreas.

Malignant disease of the pancreas is decidedly rare, and it is much rarer still to meet with such affections in early life. However, instances of congenital malignant disease—so-called "cancer"—have been reported by Arnozan and Rokitansky, and Kühn has met with "cancer" in a two-year-old infant. Litten has described an enormous sarcomatous tumor that arose from the pancreas of a male infant four years old, and disseminated in the retroperitoneal lymph glands, kidneys, mesentery, and intestines. The author claims that this is the first case of sarcoma of the pancreas ever recorded as such. Israel has found "cancer" at thirteen years and Battersby at fourteen years. According to my ideas the carcinomatous nature of the disease has not been clearly established in any of the foregoing cases.

The Testis.

The malignant neoplasms of the testis, especially those of early life, are remarkable for the great frequency with which heterotopic structures—such as cartilage, bone, striped muscle, unstriped muscle, and epithelial elements, often ciliated—are found in them. If testicular neoplasms were more thoroughly examined than has hitherto been customary, probably few would be found free from such admixtures. Cartilage is more frequently present in these neoplasms than in those of any other locality. Chondrification may sometimes be associated with spindle-celled elements. The tumors arise between the epididymis and the testis, in the vicinity of the hilum. At first they are circumscribed, and by pressure indent adjacent structures. It is exactly in this position that certain teratoid and "dermoid" tumors are met with, of which some three dozen cases have been recorded. These contain all the heterotopic structures so often met with in malignant testicular neoplasms. Hence there is *prima-facie* reason for supposing that the latter originate in connection with the former. I believe, however, that this is seldom the case, for epidermoidal structures are very rarely met with in malignant testicular neoplasms.

Lovett and Councilman have reported the following very remarkable instance of malignant testicular teratoma:

An infant, three weeks old, had a large, smooth, ovoid tumor, eight inches in circumference, connected with the right testis, the cord of which was thickened. At birth the tumor was as large as a hen's egg. Castration was performed and a solid tumor, enclosing numerous cysts, was removed. The solid substance consisted of round, spindle-celled, myxomatous, and fibrous structures, enclosing chondrifying and ossifying areas, and striped muscle fibres. Of the numerous cysts some were lined with cylindrical epithelium and others with epidermoidal cells; in some of the former the cells were ciliated. Structures resembling rudimentary embryonic eye elements, with pigmentedc ells, etc., were also discovered. The child soon recovered from the effects of the operation and he remained free from local recurrence; but seven months after the operation a large soft tumor had formed over the right parietal region. An attempt was made to remove this, but it was only partially successful as the underlying bone was infiltrated. Rapid recurrence set in, and a tumor larger than the child's head soon formed. Cachexia supervened, and the patient died exhausted three months later. The enormous mass of the tumor almost completely covered the top of the head. It appeared to have started from the dura mater. Although the brain had been compressed, no symptoms were noticed during life. Except that it was of a more medullary nature, this tumor—in its gross and microscopical characters—resembled the primary testicular tumor. It contained numerous cysts, embedded in sarcomatous stroma, containing cartilage, bone, striped muscle, etc. The cysts were of the mucosal and epidermoidal types. In addition to the structures found in the primary tumor, it contained large quantities of gliomatous tissue, which may have been derived from similar elements unnoticed in the primary tumor, or from the "retinal-like mass" that was noted in connection with the ocular rudiments. For these reasons I regard the secondary tumor as a derivative of the primary one, a detached portion of which was probably carried to the head in the form of an embolus. I am especially led to this conclusion by studying such cases as Montgomery's, in which a malignant intraabdominal teratoid tumor resulted in the formation of similar complex teratoid growths in various parts of the body.

It seems probable that most malignant testicular neoplasms originate in connection with local developmental irregularities arising at a later period than those which cause fœtal inclusions. Many circumstances point to aberrant elements, connected with "rests" of the Wolffian body, as the germs whence most tumors of this kind arise. It is believed that the junction between the Wolffian tubules and the tubuli seminiferi is brought about by the forward growth of the Wolffian tubules into the hilum. At this stage fragments of the adjacent protovertebral matrix, etc., may readily be dislocated, and so become embedded in the evolving organ, where they constitute the "rests" above mentioned. The difference between ovarian and testicular development in this respect may be the reason why these heterotopic elements are absent from ovarian neoplasms; at any rate, the ovaries are developed in just as close proximity to the protovertebral matrix as the testes, and if there were not some special difference in their ontogeny, the former would be just as liable to these heterotopic inclusions as the latter.

In the malignant testicular tumors of early life sarcomatous elements usually predominate; but sometimes cartilaginous, osseous, rhabdomyomatous, leiomyomatous, or epithelial elements are chiefly present. In a congenital case seen by Weber—in which cartilage largely predominated—the tumor, which at birth was the size of a pigeon's egg, increased in fifteen months to the size of a goose's egg.

Examples in which bone predominated have been reported by Johnston and others. In Johnston's case the tumor was first noticed when the patient was three months old; and in addition to the osseous structures there were numerous cysts lined by columnar ciliated epithelium embedded in fibrocellular stroma. Neumann has also described an ossifying tumor.

Rhabdomyomatous structures comprised the bulk of the tumor in cases reported by Neumann in a child three and one-half years old, and by Ribbert in boys of thirteen and fourteen. Rokitansky, Billroth, Arnold, and others have published similar cases.

Glandular elements were conspicuous in cases recorded by Parker in an infant three months old, by Hertzberg and Butlin in children two years old, by Reboul in a boy of six, etc. Of fifteen adenosarcomata tabulated by Eve three were in infants. Such neoplasms are often erroneously designated "cancer." In a remarkable congenital case reported by Rogers, both testes, which had not descended, were thus affected, causing a large intraabdominal tumor, which proved a serious obstacle to delivery.

Of 51 malignant testicular neoplasms analyzed by Curling, in 5 the disease began during the first quinquenniad, and in 1 between fifteen and twenty. Of 41 testicular sarcomata tabulated by Butlin, 5 belong to the first quinquenniad, the youngest being eight months old; 4 to the second quinquenniad, and only 1 to the third. These tumors are often bilateral; of 15 cases in infants analyzed by Schubert, both testes were involved in 3.

I have seen adenomyxosarcoma of the left testis in a youth nineteen and a half years old, who died with acute dissemination sixteen days after castration. Metastatic nodules were found in the skin, eye, triceps muscle, both lungs, liver, both kidneys, jejunum and other parts of the small as well as the large intestine, and in the retroperitoneal glands.

Marchand has demonstrated the presence of suprarenal "rests" in the epididymis, but it has not yet been shown that tumors have arisen from them. Edwards has reported sarcoma of the epididymis in a child of four, and Walsham myxosarcoma of the spermatic cord in an infant aged thirteen months, and in a child four years old.

The testicular sarcomata of early life are apt to progress rapidly, to invade the cord and adjacent glands, and to cause metastases; moreover, they often recur after removal.

The Ovary.

A large proportion of the malignant neoplasms of the ovary, which are rare, occur in infants and young children. Of twelve cases in which tumors of this kind were extirpated Aldibert reports that six were in children between the ages of seven and nine years, and one child was only four years old. These neoplasms are invariably sarcomatous; and both ovaries are often affected. Virchow has met with congenital myxosarcoma. Cases have been recorded by Brown at nine months, Hoffmann at twenty-two months, Cameron at three and a half years, Marchand at four years, Croom and Lucas at seven years, Leopold, Chauveau, and Chenoworth at eight years, Malins at nine years, Wagner at ten years, Kelly at twelve years, Wagner at thirteen years, Spencer Wells at thirteen and three-quarter years, Smith and Leopold at fourteen years, and by Szabo at fifteen years. Doran has found papillomatous cysts in the ovary of a seven-months' fœtus. In the cases recorded by Croom, Lucas, and Hoffmann precocious sexual development was associated with the ovarian tumors.

Ovarian dermoid cysts have often been met with at birth, in infancy, and in childhood; but I am not aware that at such early ages malignant disease has been observed in connection with them. Doran has, however, seen an instance of this at seventeen years, Hauke at fifteen years; and Jacobsen and Jessop have reported examples at thirteen.

Several examples of alleged "cancer" of the ovaries in infancy and childhood have been published; but so little that is reliable is known of ovarian cancer that I hesitate to accept them as such. In tumors of this kind glandular structures and consequently cysts predominate. Cases of this kind have been reported by Mengershausen, Leopold, Gussenbauer, Krukenberg (all at eight years), Guttmann (at fourteen and a half), Doran (at fifteen), Kahlden, and Hennig. Some malignant ovarian tumors probably arise from supernumerary ovarian structures, which are fairly common in the vicinity of the ovary. It is noteworthy that these ovarian neoplasms, unlike their congeners of the testis, hardly ever contain heterotopic structures such as cartilage and striped muscle—at least, I know of no recent instance in which their presence has been demonstrated.

Such structures are common in ovarian, teratoid, and dermoid tumors; hence it may be inferred that sarcomata of the ovary, like their testicular congeners, seldom arise in connection with defects of this kind. Undoubted instances of the origination of malignant disease from teratoid and dermoid tumors other than those above mentioned have, however, been reported.

In an androgynous female of sixteen, Virchow and Litten found a malignant teratoid cystoma of the right ovary, with bilateral cystic hydrocele of the processus vaginalis. The tumor was multilocular, and included several small dermoid cysts. Its stroma contained medullated nerve fibres, unstriped muscle elements, and hyaline cartilage, in addition to round-celled sarcomatous, myxomatous, and fibrous structures. The secondary growths in the liver consisted of a myxosarcomatous matrix, in which were embedded numerous adenomatous cysts, just like those met with in the primary tumor.

The Uterus.

In early life the uterus, like the mamma, is very seldom attacked by any form of malignant disease. This relative immunity, which contrasts so markedly with their subsequent proclivity to diseases of this type, is probably due to the rudimentary condition of these organs at birth and during infancy; for it must be remembered that the essential features of their anatomy are almost entirely of post-embryonic origin.

Although no example of congenital malignant disease of the uterus has hitherto been recorded, it is probable that most infantile forms of the disease are of blastogenic origin. Of seventy-three uterine sarcomata tabulated by Gusserow, four originated under the age of twenty years. Most cases of this kind present as polypoid tumors springing from the inferior segment of the uterus; they are usually multiple *ab initio*, and they are often accompanied by polypoid excrescences of the adjacent mucosa. Not infrequently they contain various heterotopic elements, such as striped muscle tissue, epithelial islets, etc. In these and in other respects they much resemble the analogous growths met with in the vagina of children; and, as a matter of fact, both organs are occasionally thus affected as well as the urethra and bladder. It is probable that these neoplasms arise from aberrant cellular elements displaced from their normal connections during the development of the part. As a rule they recur rapidly after removal and are highly malignant. Clay was one of the first British surgeons, who specially called attention to this type of disease.

In C. T. Smith's case, a child three and three-quarter years old had a tumor of this kind, of eight months' duration, which projected into the vagina. It recurred rapidly after excision, and two months later it was removed again. Recurrence soon followed, and an abdominal tumor then appeared, which rapidly increased. The girl died thirty-three days after the last operation. At the necropsy the abdomen was found distended by a large purplish tumor connected with the uterus. The peritoneal cavity contained fluid. There was double pyonephrosis, with acute nephritis and miliary abscesses of the right kidney. The tumor, which weighed thirty-one ounces, was a round-celled sarcoma of liver-like aspect. The mucosa of the uterus and vagina was thickly studded with small mucous polypi.

In a case recently recorded by Henry Smith in an infant one and a half years old a tumor the size of a walnut presented at the vulva. The uterus was enlarged to the adult size. The tumor was connected by a pedicle with the cervix uteri. The whole interior of the uterus was thickly studded with polypoid excrescences, each about the size of a pea, which looked just like ordinary mucous polypi. The tumor was cut away and the polypi were curetted. When last heard of, one year after the operation, the patient was well.

Similar instances have been reported by Farnsworth at thirteen months, by Pick at two years, by Ahlfeld at three years and four months, and at various ages by Clay and Pick.

Many of the malignant tumors of infancy and early life contain epithelial or pseudoepithelial elements, and this has often led to their being called "cancer"; but it is now generally recognized that all such neoplasms really are sarcomatous. Several instances of this kind have been reported as occurring in the uterus.

Rosenstein's patient, only two years old, came under treatment for dysuria, caused by an intraabdominal tumor, which reached far above the pubes. The inguinal glands were enlarged. She died shortly afterwards. At the necropsy a large mass of new growth was found in connection with the fundus uteri. There were several nodules of similar growth on the peritoneal surface of the bladder. The uterine mucosa was unaffected, as well as that of the tubes and vagina. Both ovaries were normal. Histologically, the tumor consisted of a spindle-celled stroma, the meshes of which contained large, polymorphous epithelioid cells. It is described by the author as "carcino-sarcoma." This anomalous neoplasm appears to me to approximate more closely to angiosarcoma than to any other well-recognized type.

Similar cases have been reported by Laidley at two and one-half years, and by Barnes at nine and ten years respectively.

Instances of uterine sarcoma of the ordinary adult type have been reported by Simpson at eleven years, and by Zweifel at thirteen years.

The Vagina.

The chief feature in the neoplastic pathogeny of the vagina in early life is the great relative frequency with which multiple polypoid sarcomata arise from its mucosa. In addition to their initial multiplicity, these tumors present other special features; they are not unfrequently congenital, and a considerable proportion of them contain striped muscle fibres. Other structures found are leiomyomatous tissue, islets of epithelial cells, and telangiectasic blood-vessels. These indications point to their origin from developmental irregularities. It will be remembered that the vagina is formed by the coalescence of two pairs of tubes at first widely separated; it is exceedingly probable that during the process of approximation and fusion fragments of muscle matrix, detached from adjacent parts, become included in the developing organ. Most of these peculiar sarcomatous tumors probably originate from dislocated cells connected with aberrant sequestrations of this kind. In addition to the vagina the uterus, urethra, bladder, and vulva may be involved, or either of these parts may be separately affected. Growths of this kind have been met with at birth by Gränicher, Chiari, Frick, Schubert, Demme, and others. An excellent specimen of this kind is preserved in the museum of St. Bartholomew's Hospital, which is thus described in the catalogue: "A large cluster of polypoid growths removed from the walls of the vagina and from the nymphæ of a child. They were of various sizes and shapes; the largest, about three inches in diameter, was attached to the upper wall of the vagina. They were soft and whitish, some being gelatinoid and pellucid. Histological examination revealed fibrocellular connective tissue."

Growths of this kind are commonest in early infancy. Hauser has met with an instance in a child six weeks old, Heckford at two months, Frick at seven months, Schuchardt and Kolisko at one year; at rather more advanced ages cases have been reported by Körner, Marsh, D'Arcy Power, Lewis Marshall, Sänger, Soltmann, Pick, Münz, Ahlfeld, and others. Demme has seen a case at seven years, and Kaschewarowa-Ruduewa one at fifteen years; but most cases are met with in children under five years. The disease may be limited to the vulva, as in cases reported by Thomas, Volkmann, and Chauveau.

Chauveau's patient was five years old when the growths were first extirpated. There was marked recurrence six weeks later; within a short time two further recurrences took place; the tumors were extirpated, but the disease soon returned and caused death. Only the vulva was involved. The disease was a spindle-celled fibrosarcoma, with epithelial islets embedded in the sarcomatous stroma. There were secondary growths in the iliac and mesenteric glands, as well as in the liver and kidney.

Cases of so-called "epithelioma" of the introitus by Lebert and Guersant in infants only three and one-half years old, and by Johannovsky at nine years, evidently belong here.

The prognosis of these early-life vaginal sarcomata is generally bad; the disease is prone to spread to adjacent parts, interfering with the outflow of urine, and so causing renal complications, which are often fatal. Lymph-gland dissemination and metastases are rare; but recurrence after removal is of great frequency. In a few cases the disease has been cured by early and thorough operation.

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The Bladder

In this organ sarcomatous tumors are occasionally met with in early life. The disease usually assumes the polypoid form, and multiple tumors are often encountered; or a polypoid condition of the mucosa accompanies the sarcomatous tumor. The condition is analogous to that which so frequently occurs in the vagina, and no doubt its origin is connected with similar developmental aberrations. These growths are commonest in the lower part of the bladder—that is to say, in the region most intimately connected, developmentally, with the vagina.

Of 252 cases tabulated by Albarran 6 were in children under ten years old. Of 35 early-life cases collected by Mariage 10 belong to the second year, 7 to the third, 5 to the fourth, 2 to the seventh, 1 to the eighth, 1 to the ninth, 2 to the twelfth, and 1 to the thirteenth year. It will thus be seen that the disease is commonest in early infancy. Of 34 cases, 19 were males and 15 females. Of these tumors 13 were sarcomata, 11 myxomata, 2 myxosarcomata, and 1 was a papilloma. In a case by Guersant the patient was twenty-two months old when first seen; but no doubt the disease usually is of congenital origin. These tumors are far more malignant than they usually appear to be.

In the Museum of the Royal College of Surgeons (No. 3693 A) is a specimen showing sarcoma of a child's bladder, which fungated through the wound made for suprapubic cystotomy, and formed a large sloughy tumor of the abdominal wall.

Dangerous renal complications, hydronephrosis, etc., are commonly caused by these growths. Such conditions tell against successful removal; so also does the multiplicity of the growths often present. Billroth has, however, successfully removed a polypoid myosarcomatous tumor (eight by five inches) from the bladder of a boy of twelve by means of a suprapubic incision. The lad appeared to be quite well a month later.

Leiomyomata, angiomata, and dermoid formations are met with in early life, but papillomata hardly ever.

The Prostate.

Of 96 primary malignant tumors of the prostate, Engelbach found that 9 originated in early life—3 in the first year and 6 in the next nine years.

Examples have been reported by Wind at eight months, by Tordens, Barth, and Bree at nine months; by Adams, Bush, and Jolly at three years, by Spanton at five years, by Wind at five and one-half years, by Barth at seventeen, and by Coupland at nineteen years.

SARCOMATA OF ADULT LIFE.

The influence of locality in determining the genesis, structure, and qualities of sarcomata is of such a predominant character that no study of their life history can be complete which ignores preexisting structural peculiarities. It is to such influences that the widely differing morphological and biological properties manifested by the sarcomata of different localities must be ascribed. Considerations of this kind are often of more importance for prognosis than mere details of histological structure. Unfortunately, the natural history of the disease, as it affects the different localities, has for the most part yet to be written.

The Bones.

The Superior Maxilla.

Sarcomata arise more frequently from the superior maxilla than from any other part of the body; yet no comprehensive study of the disease has ever been made. The following account is based on personal study of twenty-three cases. In a complex structure like the superior maxilla, it is a matter of the first importance to determine the matrix, whence the disease takes origin. Besides the bone and its periosteum, we have to consider the antrum and its lining membrane, as well the alveolar process and the tooth follicles. Most maxillary sarcomata arise in connection with the antrum into which they project. The periosteum is their commonest matrix; but cases also arise from the mucosa. Of eleven sarcomata of the antrum I was able to determine that three arose from the vicinity of the dental alveoli. In the periosteal sarcomata small, round, and spindle cells predominate; and there is generally more or less fibrillation, with occasionally ossification or even chondrification. It is rare for myeloid cells to predominate, except in tumors springing from the alveolus. In the mucosal sarcomata, myxomatous tissue and glandular elements are met with. Sarcomata also arise from the nasal process, chiefly from the periosteum of its deep aspect; of nineteen maxillary sarcomata examined by me four had this origin. In these forms spindle cells predominate, and myeloid cells are fairly common. Maxillary sarcomata hardly ever originate from the facial or external surface of the bone.

Next to the antrum, the alveolar process—in the vicinity of the tooth follicles—is the commonest seat of the disease. The tumors project externally, by the teeth, on the gums, where they are commonly known as "epulis." Similar tumors also arise from the vicinity of the crusta petrosa of the teeth.

From the clinical standpoint it is convenient to describe these *epulis* tumors apart from other maxillary sarcomata, although they differ from them only in respect to their point of origin. They generally make their first appearance as firm, smooth, elastic swellings on the alveolar margin, beneath the gum, between the necks of two contiguous teeth. They are firmly attached to the subjacent parts, and they seldom exceed a walnut in size. Their attachment is much more deeply seated than might at first sight be supposed, for they almost invariably arise from the bony septum between two alveoli. Most tumors of this kind are of periosteal origin; but not a few originate directly from the alveolar bone, which they may interpenetrate and expand. They consist of firm, fleshy-looking substance, in which fibro-spindle-celled tissue generally predominates, together with a considerable quantity of myeloid elements; and they are often partially ossified. Such ossification may be continuous or discontinuous. Exceptionally epulis may ossify so completely as to be hardly distinguishable from exostosis. Completely detached tumors (paraalveolar) are occasionally met with. Butlin describes a case of this kind, and similar tumors have been described by others.

It is probable that most of these epulis tumors arise from "rests" of the alveolar margin, detached during the process of development. Sometimes the disease is obviously connected with defective dental evolution. It accords with this that epulis may be multiple *ab initio* and congenital, while a considerable number of cases have been reported in early infancy. Most cases, however, appear during the third and fourth quinquenniads, but a goodly number also occur at more advanced ages. Both sexes are about equally liable. Left to itself epulis usually runs a very chronic course.

There is a softer form of the disease in which cellular elements of the spindle and myeloid kinds predominate, which progresses more rapidly than the ordinary fibrous form, and attains a larger size, destroying adjacent parts by "pressure atrophy." Such tumors, being very vascular and easily eroded, are apt to bleed. Like other myeloid sarcomata, these forms are very prone to recur locally, but they appear seldom, if ever, to cause metastases.

Sarcomata arising from other parts of the maxilla belong to a later period of life, very few cases being met with under twenty. Of 19 such tumors under my observation the earliest age at which the disease was first noticed was 17.4 years, the latest 77.5 years, and the mean age 46.3 years. The numbers for each quinquennial period were as follows:

From 15 to 20 years	in 2 cases.
“ 20 “ 25 “	“ 2 “
“ 25 “ 30 “	“ 1 case.
“ 35 “ 40 “	“ 2 cases.
“ 40 “ 45 “	“ 2 “
“ 50 “ 55 “	“ 4 “
“ 55 “ 60 “	“ 1 case.
“ 60 “ 65 “	“ 2 cases.
“ 65 “ 70 “	“ 1 case.
“ 70 “ 75 “	“ 1 “
“ 75 “ 80 “	“ 1 “

These tumors progress rapidly, and left to themselves they generally end fatally within a year or two. Chronic cases of more than five years' duration are comparatively rare. Of 20 patients coming under treatment, the duration of the disease had been as follows:

From 1 to 6 months	in 7 cases.
“ 6 “ 12 “	“ 6 “
“ 1 “ 2 years	“ 3 “
“ 2 “ 3 “	“ 2 “
10 years	“ 1 case.
18 “	“ 1 “

Most of these tumors were mixed-celled fibrosarcomata, in which round and spindle-celled elements predominated. In the case of ten years' duration the tumor was an ossifying spindle-celled sarcoma; and in the case of eighteen years' duration a mixed-celled periosteal sarcoma of the nasal process.

Of 8 cases that ended fatally under my observation, the longest duration of the disease was 33.7 months, the shortest 5.7 months, and the average duration 13 months.

The adjacent lymph glands are more frequently infiltrated than in most varieties of sarcoma. Of seventeen primary cases this was noticeable in seven; the glands first obviously involved are usually those below and in front of the root of the zygoma, and also those below the ear. Maxillary sarcoma is very prone to recur locally, even after repeated operations. A noticeable feature about them is that they seldom originate metastases. Of eight necropsies in my list, none presented metastases, although in four the lymph glands of the neck were infiltrated.

Most of those in whom the disease ran its natural course died of asthenia, one case being complicated by intracranial extension.

Maxillary sarcomata are of more frequent occurrence than maxillary carcinomata; of 7,297 carcinomata, 70 were of the maxilla, whereas of 1,081 sarcomata 102 were of the maxilla. As a contribution to the natural history of the disease I have collected the following data:

Civil State.—Of 15 women, 6 were married, 4 widowed, and 5 were single. Of 7 men, 6 were married and 1 was single.

Occupation.—Of 6 married women there were housewives 5, laundress 1, of 4 widows there were houseworkers 2, shoe-factory hand 1, nurse 1, of 5 single women there were servants 3, charwoman 1, needleworker 1. Of 6 out of the 7 men there was one each tailor, clerk, cabinetmaker, music teacher, steamship officer, and stonecutter.

Pregnancy, etc.—The married women were all fertile, and averaged 5.4 children each. Of the cases in which inquiries were made, in all the catamenia had been regular, the average at cessation being fifty years.

Previous Injury or Disease of the Part.—Of 20 cases, in 2 the disease was attributed by the patient to previous contusion; and in 2 other cases to dental caries. In the other 15 cases there was no history of any previous injury or disease of the part.

Previous Health.—Of 15 cases, the previous health had been good in 12 (with no serious illness since youth), and bad in 2. There was distinct evidence of syphilis in 3 cases.

Family History.—Of 15 families there was history of *cancer* in 2; in 1 the patient's mother died, aged forty-seven, of cancer of the uterus; in the other the patient's paternal grandfather died of "cancer of the face," and a daughter of his died, aged forty-two, of cancer of the breast. Of 15 families there was no history of *non-malignant tumors.* Of 14 families, in 5 one or more members had died of *phthisis.* Of 10 families there was history of *insanity* in 2; in both of these families there was history of phthisis as well.

Of 13 primary cases the *general condition* of the patient when first seen was as follows: Well-nourished 11, pale and emaciated 2. Of 11 patients 7 were of dark and 4 of fair complexion.

Of 8 *necropsies* the following morbid conditions were found: Extreme emaciation in 6. There were old pleural adhesions in 6 cases, with obsolete tubercle as well in 4; bronchopneumonia with pleurisy in 1 case; emphysema and congestion in 2 cases; hypostatic congestion in 1 case. In not a single case were the lungs normal. Hypertrophy of the left ventricle of the heart was found in 2 cases; thickening of the auriculoventricular valves, 1 case; mitral stenosis, 1 case; great excess of external fat, 1 case; atheroma of the aortic arch, 1 case; the heart was normal in 3 cases. Hydatid cysts of the liver existed in 2 cases; the liver was fatty in 2 cases; congested, 2 cases; gall-stones, 2 cases; irregular capsular thickening, 1 case; large and smooth, 1 case; small cyst in right lobe in 1 case; normal in 1 case. There were fibroid patches and thickening of the capsule of the spleen in 1 case; the organ was pale and soft in 1 case; normal in 6 cases. Chronic interstitial nephritis was found in 2 cases (one kidney having a double pelvis); the gland was normal in 6 cases. The brain was normal in the two cases examined. Of 5 females there were uterine myomata in 2 cases.

The Inferior Maxilla.

Many sarcomata arise from this bone, although not so many as from the superior maxilla. The alveolar process is their favorite seat, and next to that the vicinity of the angle. Most of these tumors are of periosteal origin, but a few originate within the bone. Mixed forms, in which spindle and round cells predominate, are the commonest, except in the alveolar tumor in which myeloid elements abound, and in those of central origin. Fibrifying and ossifying changes are common; but chondrification is relatively rare.

The tumors styled "epulis" are of even more frequent occurrence in the lower than in the upper jaw. Although commonest in youth, a considerable number arise later in life. In their origin, varieties, and life history they precisely resemble the corresponding tumors of the upper jaw. The following is an example of the chronic fibrous form of the disease:

A married woman, aged 60, had a firm, pedunculated, fleshy-looking tumor, the size of a small bantam's egg, which occupied the whole alveolar region of the left lower jaw, having caused absorption of most of the alveolar process. The tumor was connected by a narrow pedicle to the remains of the edentulous alveolar margin in the molar region. It was excised together with a portion of the alveolus, to which it was attached. It consisted mainly of dense fibrous tissue, the pedicle being ossified. The disease was first noticed fifteen years ago, when it presented as a pea-like nodule, projecting from the gum, in the vicinity of the stump of a carious molar tooth.

As an example of the softer and more malignant form, the following case is typical:

An unmarried woman, aged 25, a cook. On examination, a firm, smooth swelling, the size of a hazelnut, was found within the alveolus of the left lower jaw, in the situation of the socket of the second bicuspid tooth. The alveolus bulged. There was no enlargement of the adjacent lymph glands. Eighteen months ago she first noticed a small hard swelling over the external aspect of the root of the stump of the second bicuspid tooth. The tumor, having attained the size of a hazelnut, was cut off, and the stump extracted. Three months later recurrence was noticed. Soon afterwards the recurrent disease was excised. This last operation was soon followed by a fresh growth, whence the present tumor has developed. The adjacent teeth were extracted, and the tumor was removed, together with a considerable portion of the alveolus, whence it grew. The tumor was of succulent whitish structure, consisting of small, spindle-celled elements, with a moderate amount of fibrous intercellular substance, and here and there calcification was in progress.

A still more dangerous form is illustrated by the following case from the University College Hospital reports:

A girl of 15 years, whose mother died of cancer of the breast, and who had lost a brother and sister from "cancer" of the leg, came under treatment with a slightly bossy, pinkish growth, which projected from the outer surface of the gum of the left lower jaw, between the bicuspid and molar teeth. The submaxillary lymph glands were enlarged. A swelling was first noticed, about three months previously, in the site of the present tumor. There was no history of injury or other known cause for the growth. The tumor was removed but recurred four times, a fungating mass quickly filling up the gap made by each operation. At last the entire half of the bone was excised, together with the tumor, leaving only the articular end. Six weeks later there was further extensive recurrence, whence an enormous fungating growth sprang, which hung down on to the chest, and at the same time both cheeks became infiltrated. The girl died of asthenia, seven months after the first operation. The tumor consisted of a softish, pale pinkish substance, composed of closely packed large round and oval cells in a finely fibrillated matrix. It contained numerous thin-walled blood-vessels.

Most sarcomata arising from other parts of the bone are of periosteal origin. They are commonest in middle-aged persons. They infiltrate the adjacent parts, are very prone to recur, but seldom cause metastases. Occasionally they disseminate in the adjacent lymph glands. Like their congeners of the upper jaw they generally run a rapid course, death resulting from asthenia.

According to my experience myeloid tumors are rare in adults, except in connection with the alveolus; they run a more chronic course than the periosteal tumors.

THE LONG BONES.

A very large number of sarcomata arise from the long bones, those of the upper extremity being much less frequently affected than those of the lower. Of 111 cases in my list, 91 originated from the lower extremity—femur 61, tibia 19, and fibula 11; and only 28 from the upper—humerus 22, ulna 3, and radius 3. It thus appears that the femur and humerus are the bones most frequently affected, and next comes the tibia. Mine are consecutive cases and consequently more reliable for establishing ratios than promiscuously gathered cases. Most of the statistics based on the latter contain more tibial than humeral sarcomata (Gross, Butlin).

The kind of tumor and its qualities are greatly influenced by the locality whence it originates, and by its matrix. Such considerations are often of more importance for prognosis, even than histological structure. Thus sarcomata of the femur and humerus run a more rapid and malignant course than their congeners in the tibia, ulna, and radius. This appears to me to be due to the comparatively large quantity of young cellular elements still capable of active growth and development comprised in these bones.

Sarcomata of the long bones originate either from the periosteum or from the medulla. According to my experience periosteal tumors are of very much commoner occurrence than central ones—at least four times as common.

In the immediate vicinity of these bones, but completely detached from them, tumors are occasionally met with resembling periosteal sarcomata. These paraosteal tumors are, no doubt, derived from "rests" of the periosteum of the adjacent bone.

There are, however, many cases in which it cannot certainly be determined whether the disease is of periosteal or medullary origin, and this is especially the case with tumors arising from the articular extremities of bones in the vicinity of joints, such as the knee. In such localities the marrow is just as much concerned as the periosteum in the growth of the bone.

In the periosteal tumors elongated, transversely striated cells, just like young muscle cells, are not infrequently met with. These are probably derived from rhabdomyomatous elements, sequestrated from the adjacent muscle matrix during embryonic life. The frequent presence of cartilaginous elements in these tumors is of similar significance. Taken together with the occurrence of paraosteal tumors, these conditions indicate that the germs of many periosteal sarcomata are of embryonic origin. Such tumors progress more rapidly and disseminate more frequently than their medullary congeners. Moreover, there are morphological differences. The periosteal tumors are of firm texture and whitish or yellowish, having marked tendency to fibrillation, calcification, ossification, and chondrification, whereas the central tumors are comparatively soft and reddish, often having a quasi-alveolar aspect; and they rarely ossify or chondrify. Their structure tends to take after that of the medulla—the young red medulla—whence they originate. They are so rich in blood-vessels that they not unfrequently pulsate, and it is to anomalous development of the blood-vessels that the cysts, so often met with, are due.

In periosteal sarcomata mixed-celled forms predominate, chiefly of the spindle- and round-celled types; but nearly as often either spindle or round cells prevail. In the central forms myeloid cells generally predominate, with some admixture of spindle or round cells.

Certain portions of individual bones are much more prone to originate sarcomata than others. The lower end of the femur, the upper ends of the tibia and fibula, the upper end of the humerus, and the lower ends of the radius and ulna, these are the seats of predilection. This special proclivity of certain localities is more pronounced in the central than in the periosteal forms, which not unfrequently arise from various parts of the diaphysis. These tumors are commonest where growth is most active.

Sarcomata occasionally originate in connection with preëxisting diseases of the bone, such as multiple exostoses. I have seen a collier, aged twenty-four, subject to exostoses since birth, with a very large chondrifying and ossifying sarcoma of the right innominate bone, which developed from one of several exostoses there in the course of six months. Chiari has reported a similar case.

Periosteal sarcomata usually run a rapid course; in a relatively short time large tumors are formed. They infiltrate adjacent parts and originate accessory tumors there. In a certain small proportion of cases, which varies for different bones, they disseminate in the adjacent lymph glands; much more commonly they cause metastases in the lungs, liver, kidneys, other bones, and elsewhere.

When only several bones are affected, I believe we generally have to do with multiple outbreaks of the disease rather than with dissemination from a primary focus. Recurrences after extirpation are common. Thus periosteal sarcomata must be regarded as malignant and dangerous tumors. They are commonest in young adults, both sexes being liable, males rather more so than females.

With regard to the central tumors, the average age at which they appear is higher than that for the periosteal forms. They are common in youth, commonest of all in adult age; in middle life a considerable number of cases occur, after which they are decidedly rare.

They are of rather more frequent occurrence in males than in females. The lower end of the femur and the upper end of the tibia are by far the commonest seats of myeloid tumors. Of seventy cases tabulated by Gross, no less than thirty-eight thus originated.

They progress much more slowly than the periosteal forms, and are far less malignant. Infiltration of adjacent parts occasionally takes place, but much less frequently than in the periosteal disease. Accessory nodules rarely develop, and it is still rarer for adjacent lymph glands to be invaded. Very rarely indeed do myeloid tumors cause metastases, but undoubtedly this does occasionally happen. Recurrences are frequent, especially after incomplete operations.

I have elsewhere called attention to the occasional development of sarcomata at the seat of fractures, "callus sarcomata," and have referred in general terms to the influence of traumatism in the etiology of the disease. In sarcomata of the long bones the patients frequently assign the disease to some form of injury. The fact remains, however, the bones most prone to fractures are not those in which sarcomata are commonest. Thus of 2,393 consecutive fractures of the bones of the lower extremity, in 952 (males, 746; females, 206) the tibia and fibula were affected, in 311 (males, 245; females, 66) the tibia alone, in 441 the fibula alone (males, 362; females, 79); and in 689 the femur (males, 445; females, 244). Neither is the sex proportion of sarcomata what it would be, if the disease were really due to fractures; for whereas males are only slightly more prone to these tumors than females, their liability to fractures is more than three times as great, viz., as 1,798 to 595. Again, most fractures of the leg implicate both bones, but sarcomata of the leg bones seldom arise simultaneously from both bones. Moreover the usual seats of fractures—the lower parts of the leg bones, the shaft and upper extremity of the femur—are just the localities where sarcomata are least prone to develop. It is evident, therefore, that traumata play only a secondary rôle in the causation of sarcomata of the long bones.

Sarcoma of the long bones usually begins as a solitary tumor, but recently many instances have been reported in which sarcomatous tumors have arisen independently in more than a single bone. Central tumors have special proclivity to this kind of multiplicity. Such manifestations are usually associated with certain forms of constitutional disease, causing debility; and especially with conditions in which the stress of the morbid process falls on the skeleton, such as osteitis deformans, rheumatoid arthritis, osteomalacia, certain post-puerperal conditions, diabetes, pernicious anæmia, syphilis, etc.

Paget, Seegelken, Nasse, Coats, Wherry, and others have epecially called attention to these manifestations. The following is an epitome of a remarkable case by Wherry:

A carpenter, aged 56, had two distinct fractures of the lower third of his right tibia about three inches apart, with a rounded swelling between the breaks, the fibula being normal. He had suffered for several months previously with a "rheumatic" affection of the knee, and three months ago he broke this same tibia in getting off a night stool. The swelling between the fracture was diagnosed as a sarcoma. Well-marked symptoms of arthritis deformans were present. The head was greatly enlarged, owing to uniform thickening of the bones of the cranial vault. His spine was unduly arched forwards and stiff.

The limb was amputated through the knee-joint. When the patient died some time afterwards, it was found that, besides the tibia, nearly all the other long bones were affected with sarcomatous tumors, and riddled with holes thereby. There were also many tumors of this kind in the cranial bones, which were enormously thickened from osteoporosis. In the dorsal spine the lesions of osteitis deformans were very marked. The sarcomatous growths, in all places, seemed to be of central origin, forming large holes in the bones by their growth. The only evidence of dissemination was a secondary tumor in the right groin.

The Breast.

Sarcoma of the breast is a rather rare disease. The relative liability of the female breast to sarcomatous growths is much below the average for the body in general; 9.4 per cent. of the body neoplasms being sarcomatous, whereas only 3.9 per cent. of female breast neoplasms are of this nature. The feature that more than any other especially attracts attention in connection with this disease is the great rarity of its occurrence as compared with cancer. Of 2,397 consecutive neoplasms of the female breast analyzed by me, 1,863, or 77.7 per cent., were cancers; while only 94, or 3.9 per cent., were sarcomata. This shows the much greater stability of the parablastic as compared with the archiblastic elements of the gland.

The great majority of mammary sarcomata arise in the immediate vicinity of the small ducts (adenosarcomata); only rarely do they originate elsewhere (pure sarcomata). This is the more remarkable when we recollect the great abundance of fibroadipose tissue that goes to make up the breast, which elsewhere is such a favorite starting-point for these growths. Moreover, the mammary integument enjoys even more complete exemption from sarcoma than it does from carcinoma; for with the exception of a few rare cases of melanoma and keloid, I know of hardly any other instances of sarcoma originating from it. The matrix tissue of the initial proliferative changes usually is the layer of hyaline substance immediately surrounding the epithelial investment of the small ducts, which is but a myxomatous modification of the adjacent connective tissue, consisting of a network of flattened, branching, nucleated cells, embedded in hyaline stroma. Owing to the intimate genetic relationship thus subsisting between the morbid growth and the glandular structures, the latter are usually involved in sarcomatous neoplasms. This close association of the disease with the glandular elements seems to indicate that it is in some way an outcome of functional aberration.

The question has been much discussed whether the glandular structures met with under these circumstances are of neoplastic origin, or whether they are merely the outcome of the mechanical distortion of preëxisting structures. From the fact that they have often been found, several inches long, within intracystic growths, it seems to me that their ectasic origin—in such cases at least—must be admitted. Nevertheless, it seems certain, from considerations presently to be mentioned, that these proliferous glandular structures do not form an essential element of the disease. The term adenosarcoma, given by Billroth to growths thus constituted, is, however, a good one, and it ought to be retained. Some idea of the relative frequency of the occurrence of adenosarcoma and pure sarcoma, and of their structural peculiarities, may be gathered from the subjoined analysis of the 30 cases comprised in my list.

In 21 of these cases the disease was primary, and in 9 recurrent. Of the primary group, 17 were adenosarcomata, and 4 contained no glandular elements. Of the adenosarcomata, in 10 there were cysts with intracystic growths, and in 7 no cysts were obvious to the naked eye. Of the cystic cases, in 3 the sarcomatous disease presented as round and spindle-celled tissue, in 2 it was round-celled, in 1 round-celled and myxomatous, in 1 spindle-celled, and in 3 cases its exact characters were not specified. Of the non-cystic cases, in 4 spindle cells, in 2 spindle and round cells, and in 1 round cells alone, predominated.

It will be gathered from this that in the cystic adenosarcomata round cells predominate, whereas in the non-cystic forms spindle cells are of more frequent occurrence.

Of the 4 primary sarcomata in which no glandular elements were found, 2 were mainly composed of round and spindle cells, 1 of round cells, and 1 was an alveolar sarcoma.

Of the recurrent group, in 2 cases the neoplasms contained gland elements, and in 7 none could be found. Of the latter cases, in 5 the new growth was round-celled, in 1 spindle-celled, and in 1 alveolar. Of the former cases, in 1 the sarcomatous tissue was round-celled, and in the other its exact character was not stated.

All the usual varieties of sarcomatous disease, met with in other parts of the body, are also found in the breast. The immense majority of these neoplasms consist mainly of round or spindle-celled structures; and, according to my observations, it is commoner to find a mixture of these two forms than either of them separately. Thus, of 19 consecutive primary cases, in 7 round and spindle cells predominated, in 6 round cells (with myxomatous tissue in 1), in 5 spindle cells, and 1 was so-called alveolar sarcoma. In the cases analyzed by Gross, spindle-celled forms were by far the most numerous; he estimates the percentage proportions as—spindle-celled 68, round-celled 27, and myeloid 5.

ADENOSARCOMA.

What gives a certain peculiarity to sarcomata of the breast is the frequency with which glandular elements are incorporated in their structure. Although this admixture makes no essential difference in the nature of the disease, yet it often causes the form assumed by the neoplasm to be strangely modified, through the development of cysts and intracystic growths.

It is generally agreed that adenosarcomata of the breast are of much commoner occurrence than pure sarcomata, but no one, so far as I know, has furnished precise data. According to my investigations, the proportion is about eighty per cent. of the former to twenty per cent. of the latter. This indicates a much larger proportion of pure sarcomata than has hitherto been generally believed.

As in mammary cancer, the initial lesion in these growths generally is a small, hard, solitary nodule. Of the seventeen primary cases in my list, in only one did the first obvious manifestation consist of two distinct nodules. Of one hundred and fifty-six cases, Gross found multiple nodules in seven; in one of these there were four nodules in one breast, and one in the other. The question of the origin of mammary sarcomata from non-malignant neoplasms I have elsewhere discussed.

In women, cancer and non-malignant neoplasms arise more frequently from the left than from the right breast. According to Schuoler, this is also the case with sarcoma, for of 35 cases, 21 were of the left and 14 of the right side. Of my 19 cases, 12 were of the right gland and only 7 of the left. Both breasts are occasionally simultaneously affected; this happened in 3 out of Gross' 156 cases, and of Schuoler's 40 cases, 4 were double. In a case reported by Delbarre, small round-celled mammary sarcoma was associated with similar ovarian disease.

As compared with cancer, it appears that sarcomata arise less frequently from the peripheral parts of the gland; for of 17 cases in my list, 9 were of central and 8 of peripheral origin; of the latter, 3 sprang from the axillary and lower segment of the gland, 2 from its axillary and upper segment, 2 from its upper, and 1 from its lower segment. Forbes mentions a case in which the disease originated from a supernumerary mammary sequestration; and most axillary sarcomata in women have a similar origin.

At an early stage of the disease, the initial proliferating cellular aggregate, together with its contained glandular elements, that constitutes the germ of the future tumor, becomes separated from the surrounding structures by the differentiation of a fibrous capsule, which soon completely isolates it. By the continuous proliferation and differentiation of these cells and their descendants, as in normal development, the tumor increases in size. This being so, there must, of course, be new formation of glandular, as well as of connective-tissue elements. Another consequence of this mode of development is that fatty tissue is never found in the midst of the morbid mass, as in cancer in which a capsule does not form. As the tumor increases in size, it pushes aside the surrounding parts; and where these hinder its progress, they are destroyed by pressure atrophy. The form ultimately assumed by the new growth depends much upon the evolution of its glandular elements. When these remain comparatively unaltered, non-cystic solid tumors of no great size result; but when they dilate and form cysts, large tumors, complicated with intracystic growths, commonly ensue. According to my observations, the majority of mammary adenosarcomata are of the cystic kind, the proportion being fifty-nine per cent. of the former to forty-one per cent. of the latter.

These tumors are abundantly supplied with blood-vessels, which are often not only unduly numerous, but also unduly large and otherwise malformed. Most of them may be regarded as imperfect capillaries, but veins are also numerous and arteries exist. They are derived by ectasis from the preëxisting vessels. In soft, cellular tumors, the vascular walls, being very thin and ill-supported, readily dilate and even rupture; whereas in the hard, fibroid kinds of sarcomatous new growths these structures play a much less prominent part.

The *non-cystic* growths usually present as lobulated encapsuled solid tumors, of ovoid or globular shape, varying in size from a walnut to a hen's egg. On section their appearance is whitish, fibroid, or fleshy-looking. They are generally of firm and elastic consistence, rather than hard. In the tougher varieties fibrous tissue predominates; in the softer kinds cellular elements. Interspersed throughout their substance numerous small, branched, cleft-like slits can be seen; these are the included glandular structures, in connection with which minute cysts may be noticeable.

Histological examination shows that such tumors consist mainly of fibrocellular tissue in which, according to my observations, spindle cells usually predominate. The slit-like clefts embedded in this tissue are the elongated and otherwise altered ductal structures, lined by one or several layers of subcolumnal cells. Sometimes the lumina of these structures are distended by degenerating cells and fluid accumulations. Hardly ever does one see glandular structures of this kind lined by flattened cells similar to those of the normal acini.

In the *cystic* form of the disease large, irregular, globular tumors are met with, which sometimes attain immense size. They are markedly lobulated, and their various subdivisions are irregularly nodular. Occasionally they acquire a pedunculated form. A capsule can generally be made out, but in tumors of large size it is often thin and incomplete.

The appearances on section vary much, according as the solid or cystic constituents predominate. As a rule there is revealed a multilocular structure, with which is associated a variable amount of irregularly distributed, moist, whitish-gray fleshy solid substance. The loculi are usually distended with polypoid ingrowths and a variable amount of fluid. Of the cases under my own observation, one of the smallest tumors presented on section quite a solid appearance. It was only after careful examination that it was seen to consist of numerous loculi tightly distended with solid polypoid ingrowths, without any associated fluid whatever. The sarcomatous new formation in this case was small round- and spindle-celled tissue.

Among the constituent elements of the neoplastic tissue, round cells generally predominate; frequently these are associated with spindle cells, and occasionally the latter predominate. Myeloid cells are now and then met with. Within sarcoma cells Pawlowsky, Clarke, and others have met with rounded, spore-like bodies, which they regard as parasitic protozoa; and Roncali has found blastomycetes.

The following is the only example of rhabdomyosarcoma of the breast known to me:

In an ill-developed, chlorotic girl, aged 16, with a large adenocystic sarcoma in the middle of the left breast, of nine months' duration, Billroth found, on histological examination of the tumor after removal, in addition to small round-celled sarcomatous tissue, numerous spindle-like, transversely striated muscle cells. To account for this unique phenomenon, he thinks either that we must admit the origin of these cells from the sarcoma cells, or that we must ascribe their origin to germs of transversely striated muscle tissue sequestrated during an early stage of development.

In addition to the foregoing, there is generally found a variable, but considerable, amount of fibrous intercellular substance, which is often aggregated into irregular strands. It is said to differ from the fibrous stroma of the normal and cancerous glands in that it is devoid of elastic fibres. Irregular gelatinous metaplasia is not uncommon; and in this connection pseudocysts sometimes arise. Both cells and intercellular substance are prone to fatty degeneration, which may be so extensive as to retard the progress of the disease and cause partial regression. Both of these degenerative changes give rise to yellowish discoloration, and sometimes to caseation. Hyaline metamorphosis of the stroma has also been noticed. Small calcareous deposits may be met with, but it is rare to find large areas thus affected, as in cases recorded by Dubar, Clarke, and others. Very exceptionally osseous and cartilaginous tissues have also been found in the stroma, as in cases recorded by Hacker, Wagner, Durham, Bowlby, Coats, Battle, Arnold, Pilliet, and others. Unduly numerous, enlarged, and irregularly formed blood-vessels are not very rare; and in the telangiectasic variety they predominate. These various changes have little or no influence on the course of the disease. Inflammation and suppuration may also occur.

With regard to the included glandular structures, at an early stage their cells by proliferation become unduly numerous, and as the result of their morbid activity fluids are secreted, which distend their lumina, and so finally convert them into cysts. In the next stage irregular processes of the proliferating periductal sarcomatous tissue project into the cysts, and finally form intracystic growths. These generally take the form of nodular club-shaped masses which sometimes attain great size; but quite exceptionally papillary structures are produced. Cysts of all shapes and sizes are met with. Epithelial cells of columnar type line their walls and cover over the intracystic growths. This indicates that their origin is from the small ducts rather than from the acini. These lining cells sometimes completely disappear during the growth of the tumor as the result of degenerative changes; at other times they undergo a kind of corneous transformation, forming little pearls, as in cases signalized by Borchmeyer and Schmidt. In addition to the solid ingrowths, the cysts usually contain a highly albuminous, pale, yellowish fluid, in which histological examination reveals numerous degenerating epithelial cells, corpuscles of Gluge, leucocytes, etc. Sometimes the contents form a granulofatty magma, like cheese or butter, as in the "tumeurs butyreuses" described by Velpeau. In a specimen of this disease removed during lactation Billroth found milk in the dilated glandular structures. Occasionally there is complete absence of any fluid contents, the solid ingrowths completely filling the cysts. These cysts may become inflamed and suppurate.

The rate of increase of such neoplasms is very variable, and their progress is often irregular. It happens in a certain proportion of cases that the original tumor remains small and almost stationary for a long period, and then suddenly increases rapidly without any obvious cause. The round-celled varieties are believed to progress the most rapidly, but as to this the evidence is by no means definitive. Marked local elevation of temperature not unfrequently accompanies this rapid increase, and occasionally pyrexia (Steinberger). The size attained by growths of this kind is often very considerable—in fact, cystic adenosarcomata are among the most bulky of mammary neoplasms. Specimens weighing seven, twelve, thirteen, fourteen, twenty-two, twenty-six pounds and upwards have been met with. There are several such in the Museum of the Royal College of Surgeons (Nos. 399, 399 A, etc., Pathological Series).

In tumors of great size the nipple may be more or less effaced by stretching, but it is hardly ever retracted. The superficial veins are enlarged. It often happens, when the tumors project much, that the overlying skin becomes congested and adherent; ulceration may then supervene, followed by fungation of the growth (*fungus hæmatodes*). In the event of the exposed capsule rupturing, the intracystic growths may also fungate. Even under these circumstances the skin is not often invaded by the disease.

Obvious local disseminative lesions are met with in this disease very much less frequently than in cancer, and the pectoral muscles are rarely invaded. Nevertheless, it is a mistake to regard the presence of a capsule as an infallible sign of benignancy, for as these growths increase they often overpass the limits of their capsules and invade the adjacent parts. Even when the capsule remains intact, and there is no obvious invasion of the surrounding structures, careful histological examination nevertheless often reveals tumor elements spreading out far from the main tumor. This insidious advance of the disease takes place along the walls of the blood-vessels—arteries and veins—and their adventitia, which may often be found infiltrated with sarcomatous tissue. As Virchow, with his usual perspicacity has pointed out, growths of this kind are surrounded by a zone of latent infection which usually extends far beyond their immediate limits.

The opinions that have been entertained by competent observers, during the last half-century, as to the benignancy or malignancy of mammary adenosarcomata, have been very varied. It is now, however, generally recognized that all neoplasms of this kind are of a more or less malignant nature. The comparative rarity of dissemination in the axillary glands is one of their most striking clinical features, in which they differ markedly from cancer; of twenty-four adenosarcomata in my list, there were but two instances of it. Of Poulsen's thirty-three cases, the lymph glands were involved in fifteen per cent. It is the round-celled variety of the disease that is most prone to disseminate in the glands. In two other instances the glandular enlargement noticeable was only hyperplastic.

As to whether these growths originate general disseminative lesions, very different opinions have been held. Virchow was the first who showed conclusively that most varieties have this power. He instanced a case in which the liver, lungs, mediastina, ribs, vertebræ, pelvic bones, dura mater, and sphenoid were thus implicated. The correctness of Virchow's observations has been fully borne out by subsequent investigations. Of 91 cases tabulated by Gross there were metastases in 17, or in 18.68 per cent.; and Schuoler met with metastases in 12.4 per cent. In Gross' cases the secondary lesions were situated as follows: Lungs in 10 cases, liver in 4, brain in 3, and dura mater, retroperitoneal glands, mediastinum, pleura, heart, kidney, muscles, and bones in 1 each. Gross believes that metastases are really of more frequent occurrence than the above figures would indicate.

Since these lesions mostly arise in the absence of secondary affection of the lymph system, their germs evidently enter the blood directly, in the vicinity of the primary disease, whence they are transported by the circulation to the localities where they finally develop into fresh tumors. The secondary growths differ from the primary ones in being devoid of glandular elements, which are thus shown not to be an essential part of the disease. Metastases have not been signalized in connection with the myeloid form, and only exceptionally does this variety cause dissemination in the axillary glands.

All the varieties of mammary adenosarcomata frequently recur locally after removal. Under these circumstances the recurrent growths usually contain no glandular element. This was the case in seven of the nine recurrences in my list. When glandular elements are present in the latter, it either means that the primary disease has been imperfectly extirpated, or that fragments of the gland have been left behind, which have subsequently taken on the same form of morbid activity.

Of 14 primary adenosarcomata in my list in which the breast had been removed together with the disease, local recurrence was known to have occurred in 3, or in 21.4 per cent. Schuoler met with it in 25 per cent. of his cases, and Gross in 58 per cent. In one of the above-mentioned cases in my list the patient was well and free from any return of the disease six years after the operation. In another case the patient was well and free from recurrence two and one-half years after excision of the first local recurrent growth. In three other of my cases the sarcomatous tumor was simply excised without removing the breast; in one of these there was local recurrence two years later, and in the other the patient was free from any return of the disease when last heard of, two and one-half years after the operation. In the three locally recurrent cases of my list, the disease reappeared three months, nine months, and two years respectively after the last operation.

According to Gross, more than half of the local recurrences (57.5 per cent.) take place during the first six months after the operation; while after the first year only 28.8 per cent. of recurrences arise, and after the first two years but 8.8 per cent. Hence the longer the period of immunity after operation the more favorable the prognosis. In his cases the average date of local recurrence was ten and a half months after operation; the latest date was four years. Return of the disease locally after operation is, however, sometimes met with at a much later period than this. Péan has recorded an instance in which, twenty-five years after amputation of the breast for adenocystic fibrosarcoma, a large tumor of similar nature formed at the primary seat, in a woman aged sixty-two. The number of recurrences is sometimes very great; as many as four, five, six, seven, twelve, and upwards have been witnessed. In a remarkable case reported by Gross, the patient underwent twenty-two operations, and fifty-four recurrent tumors were removed in the short space of four years. Hoffmann has described an instance of spindle-celled fibro-myxo-sarcoma, in which there were twelve recurrences in four years.

According to Gross, the period of immunity from recurrence is longer for spindle than for round celled forms, and it is longest of all for the myeloid variety. The recurrence of adenocystic growths sets in, as a rule, about eight months after operation, whereas the period for the non-cystic form is about thirteen months.

The disease sometimes runs a very chronic course. Of Poulsen's thirty-three cases in ten the disease had existed for five years and upwards, for ten years in three cases, for seventeen years in one case, and for forty years in two cases.

The total duration of life, in operated cases, Gross has found to be eighty-one months; ninety months for spindle-celled forms, fifty-four for round-celled ones, and one hundred and eight months for the myeloid kind.

Very acute cases are occasionally met with. Four of Poulsen's thirty-three cases were of this nature, and two of my sixteen cases. In a case reported by Linder, a few days after injury to the breast, a pseudo-inflammatory swelling formed, for which the breast was amputated seven weeks after the injury. Recurrence at once set in, of which the patient died soon afterwards.

According to Gross, the disease may supervene as early as the ninth year, and as late as the seventy-fifth, the average age of his cases being 40.6. Only 2.7 per cent. of them supervened before the sixteenth year, while 52 per cent. supervened after the fortieth year.

The average age at onset for the spindle-celled forms was 36, for the myeloid 47, and for the round-celled 48 years. Twelve per cent. of the spindle-celled cases commenced before 16. Chambert has met with a round-celled sarcoma, the size of a fowl's egg, in the right breast of a female infant, only four months old, in whom the disease was first noticed when she was five weeks old. Vieregge has reported melanotic sarcoma of the breast in a young infant.

The data relating to family history and heredity are on the whole similar to those ascertained by me to hold for cancer, and similar inferences may be drawn from them. I have seen a museum specimen of sarcoma of the breast removed from a lady whose two sisters had similar disease, also of the breast; and Paget cites the case of a lady, the victim of hard cancer of the breast (other members of her family were believed also to have died of cancer), whose three daughters all developed adenosarcoma of the breast.

Just so is it with regard to the etiological significance of previous local injury or disease, civil state, pregnancy, etc.; the conclusion from the data being that in the vast majority of cases the outbreak of the disease is entirely spontaneous, and not traceable to the immediate action of any appreciable extrinsic cause whatever. Gross found history of trauma in ten per cent. of his cases.

From such information as is available—which is somewhat limited—it may be inferred that mammary sarcomata, destitute of glandular elements, run a similar course to the corresponding varieties of adenosarcoma. They seldom originate such large tumors as the latter; nor are the tumors so lobulated and bossy. Stilling has met with examples containing cartilaginous and osseous nodules.

Alveolar Sarcoma.

Under the name of alveolar sarcoma, plexiform angiosarcoma, endothelioma, etc., certain rare forms of mammary neoplastic disease have been described, in which the glandular elements do not participate. According to recent investigations these growths arise from the endothelial cells of the adventitia, or of the lymph spaces. If we accept this view of their origin, they should be classed with the cancers, for embryological researches have shown that the endothelium is a derivative of the archiblast and not of the parablast, to which its origin has hitherto generally been ascribed.

There are many facts in the morphology and clinical history of the disease that are best explained from this standpoint. Schmidt has studied these neoplasms as they occur in the breast. He describes their gross morphological features as being very similar to those of the adenosarcomata. They differ from the latter, however, in that the overlying skin is more frequently adherent; moreover, they much more frequently disseminate in the adjacent lymph glands and in the system generally. In these respects they resemble the cancers, but unlike the latter, they generally have a pseudo-capsule, and they do not cause retraction of the nipple. In all but one of Schmidt's eleven cases the tumors were peripheral.

With regard to the relative frequency of lymph-gland dissemination, Gross says it is met with in over sixty-six per cent. of all cases; whereas Schmidt describes it as being rare. Both are, however, agreed as to the frequency of metastases. These have been found in the liver, lungs, bones, spleen, kidneys, and omentum. Local recurrences after removal are of rapid formation, and very frequently encountered.

On section a reddish-yellow structure is displayed, in which imperfect alveolation can often be made out with the naked eye, certain of the septa generally being perfectly obvious. Histological examination reveals an alveolar formation, the walls of which consist of strands of sarcoma cells grouped around fine capillary blood-vessels. Within the alveoli are large ovoid or rounded, nucleated, epithelioid cells, which are derived by proliferation from the cells lining the dilated lymph spaces within which they lie. As the intraalveolar cells increase, they often cause by their pressure obliteration of the surrounding blood-vessels, and so hyaline or myxomatous degeneration of the corresponding part of the neoplasm, which sometimes results in cystic formation.

Billroth has reported an instance of a rare variety of the disease—*myeloid alveolar sarcoma,* occurring in a multipara aged forty-two.

Under the name of *myeloid carcinoma* similar cases have been recorded by Snow and Farmakowsky.

MYXOMA.

This is a rare form of mammary neoplasm, since of my 2,397 female cases there were only two examples of it.

In their main features myxomata of the breast closely resemble sarcomata, of which they are evidently but a sub-variety. The chief pathological consequences of the histological diversity subsisting between these two forms of the disease are that the myxomata rarely originate metastases, and that they recur locally after removal much less frequently than other sarcomata. Like the latter, most myxomata originate in the immediate vicinity of the small ducts, hence they usually contain glandular structures, whence cysts with intracystic growths frequently evolve, as in the adenocystic sarcomata. Myxomata are also met with devoid of any glandular structures; these originate from the fibrofatty tissue of the organ remote from the ducts, and their structure often comprises a considerable amount of fatty tissue. In the midst of a myxomatous tumor of six years' growth, removed from the breast of a multipara aged thirty-five, Moore found a distinct lipoma.

Mammary myxomata generally present as ovoid, circumscribed, lobulated tumors, of elastic consistence, and about the size of a hen's egg. They are enclosed in a thin fibrous capsule, which isolates them from the surrounding parts. In most cases they are mobile, but not infrequently they adhere to the overlying skin, which may ulcerate, and so the growth may fungate. They do not cause retraction of the nipple, and dissemination in the axillary glands is very exceptional.

On section the myxomatous tissue seldom presents the clear, glassy appearance of pure mucous tissue, such as is typically seen in the jelly-fish; instead there is revealed a translucent, yellowish, or grayish gelatinous substance—which exudes a viscid fluid—with various opaque or semi-opaque areas irregularly scattered throughout it, due to fatty changes, etc. Histologically this tissue consists of stellate and spindle cells, which communicate by means of numerous fine processes, and the meshes of the network thus formed are filled with mucous substance. Numerous capillary blood-vessels pervade the tissue, and not infrequently round and ovoid cells are also present. Billroth found a number of lentil-like, osseous nodules in a mammary myxosarcoma, and Leloir has met with a somewhat similar condition. In some varieties the mucous element predominates, in others the cellular, and in yet others the fibrous, fatty, or vascular elements. Jüngst has seen extensive hyaline degeneration. When the neoplastic cells themselves degenerate pseudo-cysts often result. The complications arising from the cystic evolution of the included glandular structures are identical with those met with in the adenocystic sarcomata, and need not be further alluded to.

Mammary myxomata require to be treated in accordance with the same principles as mammary sarcomata. The prognosis is, however, more favorable than for the latter; for, according to Gross, local recurrences after removal are met with only in 16.6 per cent. of all cases. Occasionally they manifest highly malignant properties.

The period of life at which the disease supervenes is much the same as that for sarcoma. Ashby and Wright have figured an instance of *congenital* myxolipoma of the breast in their treatise on the diseases of children, but they give no history of the case.

SARCOMA OF THE MALE BREAST.

From such instances of sarcomatous disease of the male breast as have hitherto been recorded, it may be inferred that all the above-described varieties met with in the female breast may also be found in it, although, of course, such occurrences are of great rarity. Most of the recorded cases known to me have been pure sarcomata. Instances of this kind are to be found in my work on "Diseases of the Breast."

Croft has reported an instance of *spindle-celled sarcoma* of the male mammary region; and S. Paget, in a man aged sixty-nine, met with a *mixed-celled fibrosarcoma* the size of a cocoanut beneath the pectoralis major muscle. It recurred so rapidly after removal that death ensued in six months.

Instances of *adenocystic sarcoma* have been recorded by Birkett, Amado, and others; while Rothmann has met with an example of *alveolar sarcoma*, and Obolinsky with an *adenomyxoma*.

SARCOMA.

(SYMPTOMATOLOGY AND TREATMENT.)

BY

WILLIAM B. COLEY,

NEW YORK.

SARCOMA.

(SYMPTOMATOLOGY AND TREATMENT.)

Introduction.

WHILE it is impossible to give a clinical picture that will fit all varieties of sarcoma, it is imperative to bear in mind certain general considerations that apply to nearly all in common.

Age.—Sarcoma may occur at any age, though it is more frequently observed between the ages of twenty and fifty years. Of 207 cases personally observed by the writer:

1	occurred	under	1 year (6 months, multiple).
9	"	from	1 to 5 years.
4	"	"	5 " 10 "
10	"	"	10 " 15 "
19	"	"	15 " 20 "
20	"	"	20 " 25 "
20	"	"	25 " 30 "
34	"	"	30 " 40 "
48	"	"	40 " 50 "
26	"	"	50 " 60 "
10	"	"	60 " 70 "
2	"	"	70 " 84 "
4	"	age not stated (adults).	
Total, 207			

Eighty-three were under 30 years, 120 over 30 years, and 43 under 20 years of age. Of 136 personal cases observed by Roger Williams, only 24 were under 20 years of age. Williams states that sarcoma of long bones rarely occurs in infants. Gross found but 6 cases under 10 years of age, in 147 cases of sarcoma of long bones. Of 119 cases collected by Butlin and Colby, 3 were under 5 years and 3 between 5 and 10 years; of my 10 personal cases of sarcoma of femur, 4 were in children under 10 years, one was aged 5 years, one was 6 years, one was 11 years, and another was 12 years. My own series of cases contains an unusual number of sarcomata in infants and children. The youngest case was a very large multiple sarcoma in an infant, aged six months; the largest tumor, situated in the soft parts of the back, was the size of a cocoanut, had been noticed soon after birth, and was evidently of congenital origin. The next case, in point of age, was a child one and one-half years old, with an enormous sarcoma of the ilium (*vide* illustration). The growth here was not congenital, having been noticed but six weeks; during this time it had reached a size larger than the infant's head, and extended from the middle of the thigh to the crest of the ilium. The movement of the hip-joint was much restricted. The general health at the time of examination, January 18th, 1897, was but little impaired; the tumor grew with great rapidity, and death occurred on the 13th of March, 1897, the entire duration of the disease having been but three and one-half months. Another child, aged two years, had a round-celled sarcoma of the orbit that ran a very rapid course; another, aged five years, had a round-celled sarcoma of the lower lip, which recurred twice after operation, and which disappeared under the mixed toxins of erysipelas and bacillus prodigiosus, and remains well at present, one and one-half years; another child, aged five years, had a large sarcoma of the kidney. Prompt recurrence followed abdominal nephrectomy.

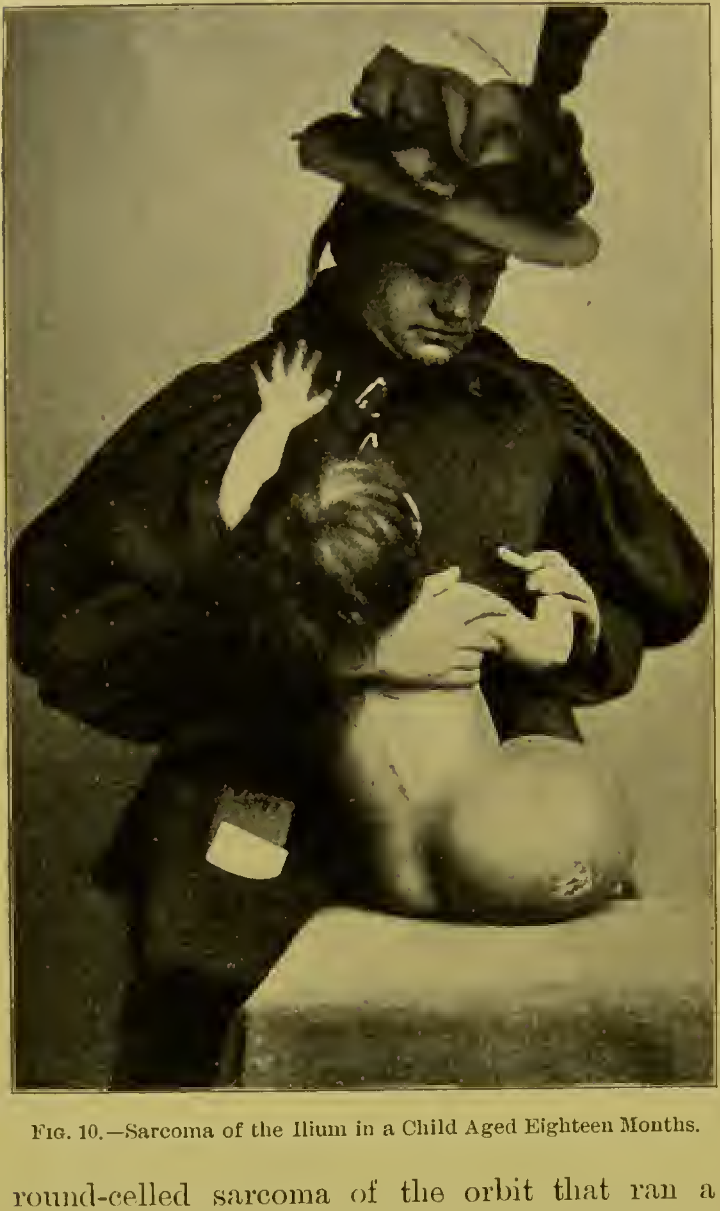
FIG. 10.—Sarcoma of the Ilium in a Child Aged Eighteen Months.

The youngest patient with sarcoma of the femur was a girl five years of age. In all the cases of children, no matter what the type of cell, the disease seemed more malignant than in adults and ran a far more rapid course.

Sex.—The male sex is more liable to sarcoma than the female; of my 207 personal cases, 117 were males and 90 females.

Anatomical Situation.—A thorough knowledge of the parts of the body most prone to sarcoma, will often be of great aid in making a diagnosis. It is a remarkable fact that the disease very commonly attacks bony structures, and there is shown a preference for certain bones, especially the long bones of the lower extremity. Of my 207 cases 47 originated in bones. Of these:

10	occurred in the femur.	2	occurred in the scapula.
4	" " " tibia.	1	" " " rib.
1	" " " fibula.	1	" " " sacrum.
7	" " " ilium.	1	" " " sternum.
3	" " " vertebræ.	1	" " " metacarpus.
6	" " " superior maxilla.	2	" " " phalanx.
4	" " " inferior "	1	" " " clavicle.
2	" " " mastoid process.		

Of the soft structures, sarcoma develops more frequently in the neck than any other part of the body. My list of 207 cases contains no fewer than 16 cases of primary sarcoma of the neck. Next come the orbit with 16 cases, primary in 14, and the thigh with 13; femur, 10; the abdominal wall with 6; parotid, 8; testis, 7; breast, 6; back, 6; pharynx, 4; axilla, 5; scalp, 3; kidney, 3; hand, 5; foot, 3; skin, 1; iliac fossa, 5.

SYMPTOMATOLOGY.

If the patient were asked what first directed his attention to the site of the sarcoma, the answer would almost invariably be, a swelling or "lump." In nearly one-third of the cases there would be, as I have already stated, a history of some previous injury to the tissues in the immediate vicinity. The injury need not be a severe one, more probably a blow or contusion sufficient to cause the patient to remember it distinctly, but regarded as of little consequence at the time. In a few cases the swelling caused by the blow never disappeared, but gradually increased in size until the patient was led to consult a physician.

Character of the Swelling.—This differs greatly with the variety of sarcoma. In the spindle-celled it is often of very firm and uniform consistence, while in the round-celled it is usually much softer, more vascular, and not infrequently gives the sensation of fluctuation. In many cases it is impossible to differentiate between a soft sarcoma and an abscess, by palpation alone.

In sarcomata of high vascularity there may be pulsation, which causes the tumor to simulate closely an aneurysm. Sarcoma of the bones or periosteum is usually much harder than sarcoma of soft parts, though in most cases the consistence is not uniform.

Pain is of less importance than is generally supposed. In a very large proportion of cases of sarcoma, the tumor often attains a large size before pain becomes a prominent symptom, and in not a few cases the disease runs its entire course without any real pain. In certain cases, however, dependent chiefly on the anatomical site of the tumor, pain may be an early symptom and one of increasing importance. In my own experience, the most painful sarcomata have been in the vertebræ. I have seen but four cases, and all have been accompanied by excruciating pain. In two the disease was primary, and in the remaining two it was secondary, in one to sarcoma of the breast and the other to a melanotic sarcoma of the neck. In one, a woman aged twenty-four years, the tumor was situated in the upper dorsal region. It originated in the spinous process, and rapidly involved the body of the vertebræ, and finally the cord; she required injections of two grains of morphine every two hours—often every hour—to control the pain.

Another location in which sarcoma is likely to be painful is the antrum or superior maxilla; the orbit should also be included. Retroperitoneal sarcoma in the iliac fossa, or sarcomata starting in the ilium or sacrum, in the vicinity of the large nerve trunks, are very painful. In these cases the pain often antedates the discovery of the swelling, and the patient is usually treated for "sciatica." Very severe and obstinate pain in the region of the sciatic or crural nerve, coming on without known cause in a person previously in excellent health, should lead the physician to make a careful examination of the iliac fossæ, and to this should be added a digital examination of the rectum or vagina.

I have recently seen a case of large abscess in the right Fallopian tube, in which the pain in the leg and thigh was so severe that the patient had been treated by two excellent physicians for sciatica. Vaginal examination revealed a soft tumor of inflammatory origin, the size of the closed fist, to the right of the uterus. A sarcoma in this region would have caused the same symptoms, and might have given rise to the same mistake in diagnosis. In central sarcoma of the bone, as the disease advances, there is finally left a thin layer that produces the so-called "egg-shell" crackling sensation on palpation. Such growths are more common in the head of the tibia than in any other bone.

Diagnosis.

The conditions most likely to be mistaken for sarcoma are tumors of tuberculous or syphilitic origin, lipomata, hæmatomata, various inflammatory swellings, and carcinomata.

Tuberculous Tumors.—In certain locations, *e.g.*, in the lymphatic glands, it is sometimes impossible to make a diagnosis between sarcoma and tuberculosis; and in case of doubt it is always wiser to have the gland removed, and subjected to microscopical examination. In most cases, however, it is possible to make a correct diagnosis from the history and clinical signs. In sarcoma, the swelling is usually more rapid in its increase, and is smoother in outline than in a tuberculous tumor. It is almost always solitary, while several nodules are usually found affected in tuberculosis. Pain, which may be absent in both, is more frequently present in sarcoma. The superficial veins are usually distended in sarcoma, seldom in tuberculous tumors. "Local heat" is usually found in sarcoma, unless the tumor is situated too deeply beneath the skin for it to be detected. An increase of one to two degrees Fahrenheit has been observed; this is true only of highly vascular sarcomata, and too much importance should not be given it as a diagnostic sign.

Syphilis.—Gumma may closely simulate sarcoma, and a previous history of syphilis may aid in establishing a diagnosis. Warning is here offered, not to place absolute reliance upon the improvement following specific treatment, as settling the diagnosis in favor of syphilis. The writer has observed, at the Cancer Hospital, an indurated ulcer of the breast in a woman who gave a distinct history of syphilis, which showed such marked improvement under antisyphilitic treatment that the diagnosis was regarded as certain. After a few weeks the improvement ceased, and on removing a portion of the tissues for examination it was found that the disease was typical carcinoma. Similar cases of improvement following the use of the iodides in malignant disease, especially in sarcoma, have been observed by Dr. Robert F. Weir and others; in case of doubt an exploratory incision should always be resorted to.

Inflammatory Swellings.—These usually give a history of more rapid development, are associated with greater pain, and there is nearly always an elevation in temperature and pulse. Here, again, we need to be on our guard, for both pulse and temperature may be increased in sarcoma, and this is especially true of the rapidly developing tumors, or in cases undergoing general dissemination.

Sir William MacCormac reports a case in which "the entire thigh was occupied by a fusiform swelling, so elastic that it seemed to fluctuate. The skin was tense and pale and much warmer than that of the other limb. Effusion had taken place into the knee, and there was excessive pain. The temperature ranged from 100° in the morning to 102° or 103° at night."

I have myself observed several cases of sarcoma, in which general dissemination had taken place, with a daily rise of temperature up to 102° or 103°. Increase in pulse rate is far more common than rise of temperature in sarcoma; in fact, it is a sign of no little value in diagnosis.

The following case, recently observed in consultation with Dr. George T. Stewart, is very similar to MacCormac's, and is quite as interesting in showing the difficulties that sometimes attend the differentiation of sarcoma from inflammatory swellings:

The patient, a stout woman, aged 49 years, seven weeks before, without known cause, had first noticed pain and a feeling of discomfort about the middle and under portion of the right thigh, when sitting down. Her husband, who was a physician, was unable to feel anything until about ten days later, when there was a well-marked swelling, deeply-seated, and tender on pressure. The pain and discomfort increased rapidly, and when I first saw the case, about five weeks from the time the swelling was first noticed, the following conditions were noted: The left thigh was two inches larger than the right, the enlargement being most marked at the middle and posterior portion. Palpation showed a swelling or tumor extending from just above the popliteal space nearly to the trochanter, and about two-thirds the distance around the leg. The consistence slightly varied, but in no place could fluctuation be detected. The outline was not sharply defined and there was much tenderness on pressure. The skin was not adherent and was not changed in appearance to any marked degree. The temperature had ranged between 99.5° and 103°, and the pulse between 80 and 90. The pain was very severe. A large aspirating needle had been introduced on several occasions, but no pus had been found. Once or twice a little bloody serum was withdrawn, but microscopical examination was negative. Hæmatoma, inflammatory swelling, and sarcoma had been considered as possible diagnoses. A few days later fluctuation could be made out and exploratory incision was made in order to settle the question of diagnosis. About a quart of bloody serum escaped on cutting through the fascia. A mass, the size of the closed fist, and but slightly attached, was then removed by Dr. Stewart, with the fingers alone. It had every appearance of a partially organized blood clot and its gross appearance did not resemble sarcoma. Microscopical examination, however, showed it to be a highly vascular giant-celled sarcoma, starting probably from the periosteum. This case is given with some detail, for the reason that it clearly shows the impossibility of making a diagnosis in some cases without exploratory incision and the use of the microscope.

SPECIAL FORMS AND LOCALIZATION.

Sarcoma can be dealt with in a far more satisfactory manner if we study it with reference to its anatomical basis rather than as a general subject.

As Butlin has well pointed out, "nothing can be more absurd than an attempt to schematize a diagnosis and treatment which shall be suitable alike for tumors of the tibia and the skull, or for tumors of the pelvis and the humerus."

Before taking up sarcoma of special organs and special anatomical regions it may be well to consider the very remarkable variety of sarcoma known as melanotic. Owing to the fact that an unusually large number of cases of this form of sarcoma have come under my observation, I have had an excellent opportunity to study its clinical features.

Melanotic Sarcoma.

This form of neoplasm was recognized in the early part of this century, Laennec describing it in 1806 under the name of melanose, which term he applied to all forms of pigmented cancer. Later Virchow divided melanotic new growths into melanoma, melanotic sarcoma, and melanotic carcinoma. Since that time, as Ebermann has remarked, there has been a general tendency in the literature and statistics of these tumors to increase the class of melanotic sarcomata and proportionately decrease that of the carcinomata, the so-called mixed form of tumor, "sarcoma and carcinoma" being now but seldom mentioned.

As late as 1870, Sir James Paget stated that melanotic cancers are, with rare exceptions, medullary cancers, and Billroth also inclined to the same view.

Although this form of neoplasm is comparatively rare, its very high degree of malignancy and early disposition to form general metastases have made it a very interesting subject for investigation by pathologists and surgeons. Ebermann, of St. Petersburg, has given us the most recent and valuable papers on the subject in the *Deutsche Zeitschrift für Chirurgie*, Vol. 43, Heft III., Seite 498. He has collected the cases observed at Koenig's Hospital and private clinic in Göttingen since 1889, 15 in number. And to these he has added the 15 cases observed at the same clinic previous to 1889, and already published in the "Inaugural Dissertation" of Zimmermann. Of these 30 cases 26 were sarcomata and 4 were carcinomata. It is interesting to note that all of the cases of carcinoma occurred in

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the rectum, while only 2 of the 26 cases of sarcomata originated in this locality. Of Ebermann's 15 cases, observed since 1889, 3 were of the spindle-celled variety, 12 of the round-celled, and almost all the latter were of the alveolar type. That the skin plays a most important rôle in the etiology of melanotic growths is shown by the fact that in 20 of Ebermann's 30 cases the point of origin was in the skin or the subcutaneous tissue. Of Eiselt's large collection of 104 cases of melanotic tumors 47 originated in some portion of the eye, and 40 in the skin. Just collected 112 cases from the literature, of which 54 were primary in the skin and 26 in the eye. Out of Zimmermann's and Ebermann's 30 cases 7 started in congenital pigmented warts. The history of trauma was noted in 7 cases.

In regard to the *age* and *sex*, about one-half of the cases occurred between the ages of forty and sixty years. Yet the disease may occur in the very young or the very old. The lymphatic glands were involved in about 50 per cent. of the cases; in Ebermann's cases in all but 2 of 16.

A very complete *résumé* of the literature on the subject was given by Dietrich in the *Archiv für klinische Chirurgie*, Vol. 35, p. 289. He collected all of the cases of melanotic tumors that he was able to find in the literature from the year 1860 to 1887, and arranged them in groups according to local origin. He found 137 cases in the literature, and to these he added 8 cases observed in Czerny's clinic in Heidelberg, making a total of 145; 114 of these cases had been subjected to operation; in 31 cases no operation had been performed.

As regards locality, 28 originated in the head, 11 in the neck, 41 in the back, 48 in the extremities. The disease occurred three times more frequently in the lower extremities than in the upper.

The duration of the disease prior to operation is a very interesting point. In 12 cases the tumors had been noticed for a period of three months; in 11 from three to six months; in 6 from six to nine months; in 10 for a year, and in 26 cases from two to twenty years.

A study of the final results of these cases strongly confirms the general belief that these tumors are very malignant. Of 114 cases operated upon 81 were traced; 53 of these died, 15 were alive, but with a recurrence, while 13 were reported sound. Of the 13 cases reported sound, only 6 had remained well beyond three years. In other words, only 6 out of the total of 114 cases could reasonably be regarded as cured.

Sixteen cases of melanotic sarcoma have come under my personal observation. In 13 of these 16 cases the lymph glands were affected, usually those nearest the primary growth.

In 7 cases the starting-point of the disease was a congenital mole, and in 4 of these cases it appeared immediately after an attempt to excise the mole by means of a thread.

In 6 cases the primary growth was in the neck; in 3 in the breast near the nipple (2 cases males; the starting-point was probably in the skin and not the gland); in 1 case in the scalp; in 2 in the skin of the thigh; in 1 in the skin of the abdomen; in 1 in the eyelid, and in 1 in the matrix of the thumb.

In addition to the 3 cases apparently starting from the irritation caused by excision with thread, there is a distinct history of injury in 2 other cases.

In 10 of the 16 cases there was rapid generalization of the disease. In one case upwards of two hundred distinct tumors were excised, mostly subcutaneous. Internal metastases were noted in 4 cases, and in one of my cases in which I was able to obtain an autopsy, Dr. Buxton found every organ involved.

In 3 cases paraplegia resulted from extension of the disease to the spinal cord.

Treatment.—It is interesting to note that recurrence was in all my cases extremely rapid, a few weeks being the longest period of freedom. This fact has been mentioned by most writers on the subject, and the question of the advisability of operating at all on such growths has been seriously discussed. Inasmuch as there are a few authentic cases of cure by operation, I think it justifiable always to advise operation in cases seen early when there is a probability of being able to remove the whole tumor. Even in such cases the prognosis is exceedingly bad owing to the very early distribution of the infectious agent through the blood current. Personally I have known of but two cases of melanotic sarcoma cured by operation. One of these is an unpublished case of Dr. L. L. McArthur, of Chicago, who has very kindly given me the history of the case: The patient was a woman, aged forty-six years, who had always enjoyed excellent health. From youth she had had a small pigmented mole on the anterior surface of the left thigh about four inches below the anterior superior spine. In 1885 this began to enlarge and become painful. In the latter part of 1886 it had reached the size of a hen's egg, and was then excised by Dr. McArthur. It was flattened where resting on the fascia lata and so intimately adherent that a portion of the fascia lata was removed with the tumor. Microscopical examination showed the growth to be typical "melanosarcoma." Notwithstanding the fact that not more than a line of healthy tissue had been excised beyond the disease, no recurrence followed and the patient was well ten years later.

The second case was one of melanotic sarcoma of the nose treated by galvano-cauterization by Dr. R. P. Lincoln, of New York, in 1884. The patient was well in 1895, eleven years later.

In my paper on the erysipelas toxins in the *American Journal of the Medical Sciences* for July, 1896, I stated that this variety of sarcoma was scarcely affected by the toxin treatment. There is one case on record, however, of melanotic sarcoma having been cured by accidental erysipelas. This with the slight improvement noted in some of my cases, notably the thumb case, shows that the erysipelas toxins exert some inhibitory action on the growth, but are insufficient to control it completely.

The following are reports of some personal cases which are possessed of special interest:

Melanotic Sarcoma of the Thumb.—W. I. W——, male, aged 37 years.

Family history: Three of father's brothers died of cancer, one at the age of 55 years, of sarcoma of the scapula; a second at the age of 69 years, of cancer of the tongue; and a third, at the age of 35 years, of cancer of the tongue. Personal history: Seven years ago the patient bruised his left thumb. On December 7th, 1892, he again injured the same thumb by getting it caught in a heavy office curtain cord. It became sore at once and slowly grew worse, having an inflamed appearance. On January 15th, 1893, he consulted a physician who pronounced it a paronychia and lanced it with a pocket scalpel. The next few days it discharged slightly and was quite painful. From January 15th to February 1st it was poulticed with little effect. The patient then consulted Dr. L. L. McArthur, of Chicago, who at first regarded it as a "felon," and operated at once, removing a portion of the nail and some denuded bone beneath. The wound failed to heal. On April 15th the nail had begun to curl up and become dark colored, and the discharge had stopped. There was no increase in size, but Dr. McArthur soon suspected sarcoma, and on May 15th removed a piece of tissue for examination and found it to be melanotic sarcoma of round-celled type. On June 6th the thumb was removed and the axillary glands as well. Three of the glands, the size of olives, were found distinctly sarcomatous. On October 1st a small superficial encapsulated tumor the size of a "birdshot" was noticed three inches above the left wrist and directly over the radial artery. November 6th a similar tumor was found beneath the skin of the right side of the chest on a line with the tenth rib. On December 3d two others appeared on the left arm and forearm; all these grew slowly in size. I saw the patient in January, 1894, in consultation with Dr. W. T. Bull, and it was decided to give him a trial of the mixed toxins of erysipelas and bacillus prodigiosus, and treatment was begun January 14th, 1894. The injections were made in the arm and in different parts of the chest, chiefly in the pectoral muscles. Both the filtered and unfiltered toxins of streptococcus erysipelas and bacillus prodigiosus were used. The tumors ceased to grow while under treatment, became more loosely attached, and one apparently disappeared. At the end of a month the treatment was discontinued and the patient was advised to rest for a month or more unless evidence of further growth should occur.

One of the small tumors was removed by Dr. McArthur and examined microscopically. There was some slight evidence of degeneration and an increase in fibrous stroma. After about six weeks the tumors began to grow again, and other new ones appeared in different and widely remote parts of the body. All were just beneath the skin and felt like hard shot, varying in size from a small birdshot to a pea. They were perfectly round and enclosed in a firm capsule and of a deep bluish-black color, though the color did not show through the skin. The patient returned for treatment in April, 1894, and the toxins were given in larger doses. The effect was less marked, but there was still a certain amount of inhibitory influence on the growth of the tumors. When discontinued for a few days or given in small doses there was an increase in number and a more rapid development in those already present. The general health of the patient was perfect, and the treatment was kept up until October, 1894.

In May a mass the size of an English walnut was removed from the left axilla by Dr. Bull and myself. Later we at different times removed upwards of one hundred small tumors from different parts of the body. Dr. McArthur removed a still larger number, making a total of more than two hundred.

The remaining history is, in brief, as follows: A rapid generalization of the disease with the development of a tumor of considerable size in the middorsal portion of the spine, and lastly involvement of the abdominal viscera, ending in death in the spring of 1895.

There was no pain until a few months before death when the tumors developed in the spine, but from this time on the pain was exceedingly severe.

Melanotic Sarcoma of the Neck—Very Rapid Generalization.—M. B——, female, aged 45 years. Family history good. Personal history: Patient had always been in good health. She had had for a long time a mole on the left side of the neck. This was probably congenital. It remained stationary up to the early part of 1895 when it began to grow. In April, 1895, it was removed by Dr. E. M. Field, of Red Bank, N. J. It was then the size of a robin's egg, and was situated just beneath the ear. There was no glandular involvement apparent at that time. Within four weeks the tumor recurred in the same region and grew slowly until September 20th, 1895, when the patient was referred to me by Dr. Field and admitted to the New York Cancer Hospital. At this time there was a tumor the size of a large hen's egg in the left cervical region, rather firmly attached to the deep structures. This was removed by operation, and the tumor was found to be entirely encapsulated. So far as one could judge, the entire tumor was removed and no enlarged glands could be felt lower down (the recurrence itself was in the cervical glands). With a view of possibly preventing a recurrence the patient was kept in the hospital for four weeks and the mixed toxins of erysipelas and bacillus prodigiosus were given in large doses. She was then discharged from the hospital, apparently in perfect health. Six weeks later she developed some pains in the back and legs and was treated for rheumatism. The pains increased rapidly in severity, and on returning to the hospital for examination in January, 1896, a small tumor was discovered in the lower dorsal region of the spine (one and a half inches in diameter)—an unmistakable evidence of recurrence. The pains in the legs were very severe, and there was soon loss of sensation. These symptoms increased, and later paralysis developed, and the patient died the last of February, 1896. Autopsy showed all of the organs involved.

Microscopical examination: Mixed large round- and spindle-celled sarcoma, markedly melanotic.

Melanotic Sarcoma of the Thigh Originating in a Pigmented Mole. —W. J. D——, aged 19 years; male; single. Family history negative, except that very recently his father has developed what appears to be an epithelioma of the lip. Personal history: When a child 4 years of age, a small pigmented mole was noticed on the inner surface of the left thigh. This was very deeply pigmented and grew rapidly to the size of a hickory nut. Three years ago it was removed by thread ligature. It quickly returned at the site of the scar and grew very rapidly. Fourteen months ago the growth was very thoroughly removed, the adjacent skin and deep tissues being carefully excised in addition to the tumor. At this time there was a small lump in the groin, about the size of a cherry, which was not removed. Six months later this nodule had grown to considerable dimensions and two small tumors had recurred at the site of the original scar. The patient was admitted to St. Joseph's Hospital, Yonkers, on March 1st. Physical examination at that time showed in the scar two tumors about the size of English walnuts and of a very dark purple color. In Scarpa's triangle, on the same side, there was an irregular mass, the size of an orange, immediately over the femoral vessel. The pigmentation was sufficiently marked to show through the skin, which was apparently not affected. A larger mass could also be made out in the pelvis, apparently originating in the retroperitoneal glands. There was evidence of considerable interference with the venous circulation in the thigh. The patient's general condition was good.

The second operation was performed March 1st, 1897. The recurrent tumors with a wide margin of healthy tissue were excised. The large tumor in the groin was likewise removed together with a portion of the saphenous vein which passed through the tumor. No attempt was made to remove the mass in the pelvis. The patient made a good recovery and the wounds healed promptly by first intention. Two weeks after the operation I saw the patient in consultation with Dr. Moffet; the mass in the pelvis had become considerably larger since the operation, and the patient's general condition had depreciated. Although expecting very little if any result from the toxins of erysipelas, the injections were advised for a short period. They were given for three weeks without any apparent gain. Numerous pigmented spots shortly appeared over the surface of the body, varying in size from a pinhead to a pea and situated in the skin itself. The patient's general condition grew rapidly worse, and on August 30th, after a severe convulsion lasting six hours, the patient died. No autopsy was permitted.

Melanotic Sarcoma of the Neck.—E. W——, aged 26 years. The family history was negative. The patient had always been in good health. He had had a small pigmented mole on the neck, and as it interfered somewhat with shaving, his family physician attempted to remove it in the fall of 1894. Removal was not complete, and the mole soon began to increase in size. A thorough excision was made by Dr. Frank Hartley in the summer of 1894. Shortly afterward a second similar growth appeared on the neck and was excised. Other tumors soon developed on different parts of the body, and in a short time there was evidence of general infection, especially of the abdominal organs. On February 10th, 1895, there were numerous small tumors

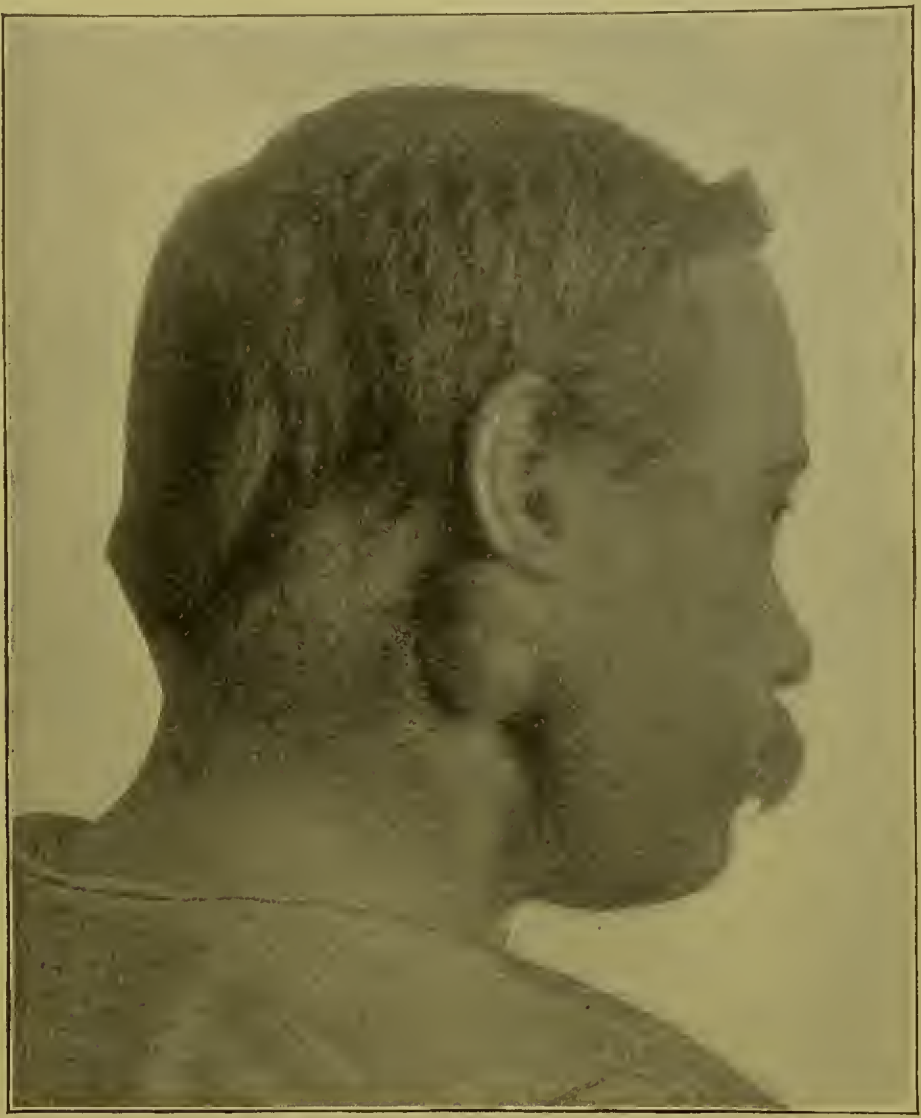

FIG. 11.—Melanotic Sarcoma of Neck.

varying in size from a hazelnut to an olive in different parts of the body. They were located in the subcutaneous tissue. The liver was enlarged and tender. The abdomen was distended and tender. The complexion was very sallow, and the patient was much prostrated. Very little hope of relief was offered by the toxins, but the treatment was tried in small doses for one month; only two or three times were the doses large enough to produce a chill. There was no perceptible effect on the progress of the disease, and the treatment was abandoned. The patient continued to grow weaker and died in April, 1895.

Sarcoma of Bones.

Sarcoma of the bony structures may be of either central or periosteal origin. In many cases it is extremely difficult to make a distinction between a central sarcoma and a periosteal, for the reason that at the time when the tumor is removed the entire bone is often involved, and its point of origin cannot accurately be determined. While sarcoma may affect any portion of the skeleton, certain bones seem to have a peculiar liability to invasion.

Concerning the relative frequency of sarcoma in the different bones, we find, according to an analysis of 165 cases of sarcoma of the long bones, published by Dr. Gross, that 67 occurred in the femur, 46 in the tibia, 21 in the humerus, 13 in the fibula, 7 in the ulna, 6 in the radius, and 1 in the ulna and radius. Of these cases only 13 were periosteal, 4 of which were of the alveolar type.

During the year 1890 I made a careful analysis of 90 unpublished cases, collected from the histories in the records of the New York Hospital during the preceding fifteen years. Of these 90 cases 68 had their origin in the soft parts, while the remaining 22 started in the bone or periosteum. Inasmuch as the subsequent history of cases of sarcoma is so very important in estimating the prognosis of the disease, I made a great effort to trace the cases, and succeeded in doing this in 44. In 26 out of these 44 cases a fatal recurrence took place at varying periods. Nine patients were found alive from three to ten years after the last operation; 4 others were alive and free from recurrence from twelve to eighteen months. Of Gross' 13 cases of periosteal sarcomata only 8 were traced, and of these 8 but 1 was known to be free from recurrence. Whether or not this was a complete cure is not known.

Clinically, the chief point of difference between the periosteal and central tumors is that the periosteal are, as a rule, more rapidly growing and, consequently, of a more malignant type. Again, the central sarcomata are more prone to invade the extremities of the bone, while the periosteal are more likely to occur some distance from the joint. The diagnosis, however, is of more pathological than clinical importance, inasmuch as the treatment for both varieties is the same.

Diagnosis.—The conditions that may simulate sarcoma and from which it is most important to differentiate it, are tumors of benign character and those of inflammatory origin. The only benign tumor that is likely to simulate sarcoma is *chondroma*. The slow growth of chondroma will usually make the diagnosis easy. Chronic inflammatory swellings or other affections of the bone of a specific or tuberculous character often render the diagnosis most difficult.

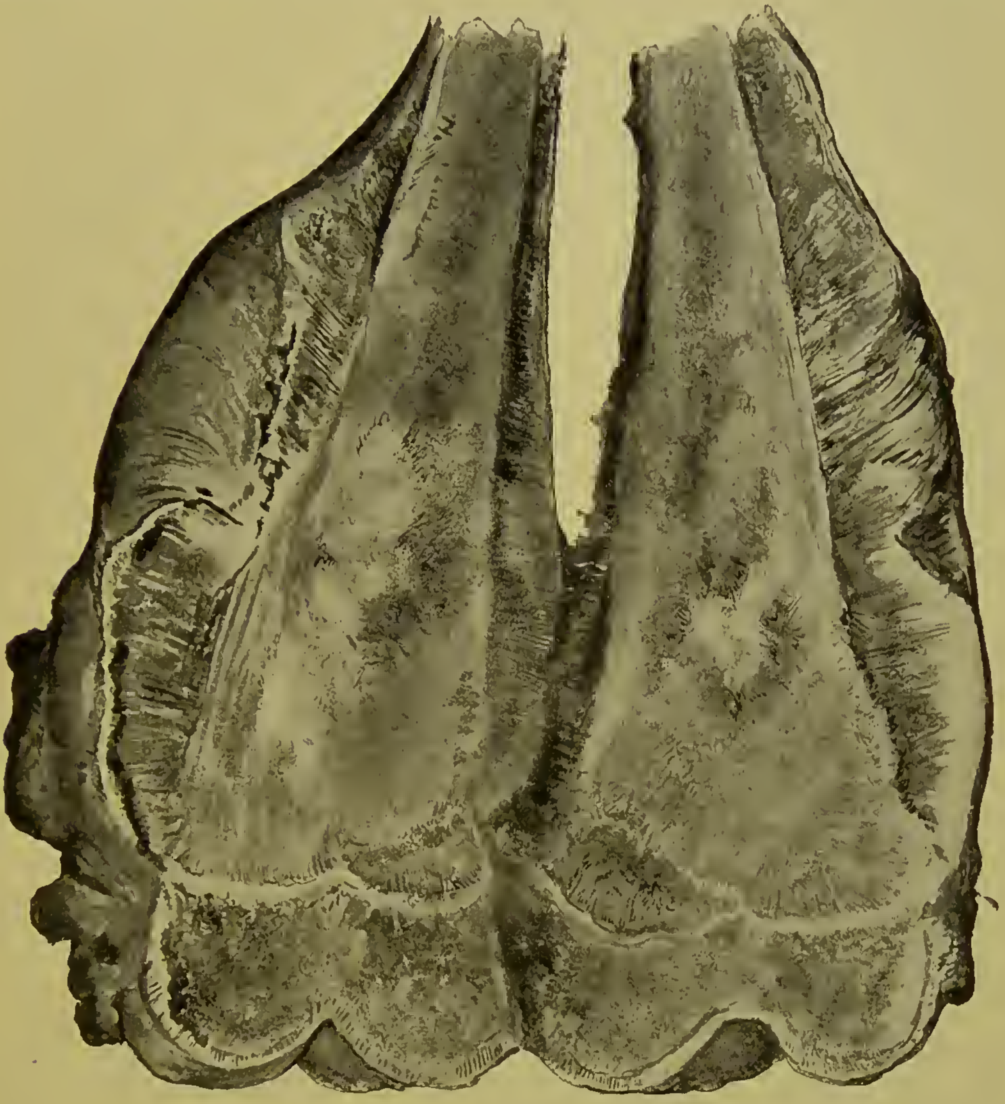

FIG. 12.—Chondrosarcoma of the Femur in a Girl Aged Thirteen Years. (Original.)

In some of the rapidly growing sarcomata of the femur, we may have present nearly all the signs of an *inflammatory tumor*, and in fact, as I have already pointed out when speaking of sarcoma in general, one occasionally finds cases in which it is absolutely impossible to make a differential diagnosis except by an exploratory incision, combined with microscopical examination. We sometimes find a subacute periostitis accompanied by marked thickening, and such a small amount of pus present that aspiration may be negative. In addition, the temperature may be but slightly elevated, and the pain no more than is frequently found in sarcoma. In such a case the diagnosis is attended with much difficulty.

Butlin cites a case of a boy, nine years of age, who had had a considerable swelling of the entire lower end of the femur, of four months' duration. Increase in size was very gradual, the temperature was but slightly raised, and pain and tenderness were also slight. All of the symptoms pointed so clearly towards sarcoma that this was the unanimous diagnosis of the surgical staff of St. Bartholomew's Hospital. An exploration, with a view to amputation, revealed a chronic inflammation of the bone and periosteum.

Tuberculous disease, especially of the tibia or lower portion of the femur, not infrequently is mistaken for sarcoma. The more chronic history of tuberculous disease, together with the fact that the region of the joint is seldom affected in sarcoma, will usually enable us to make a correct diagnosis. If there is any doubt after a very careful examination, it is far better to settle the diagnosis by an exploratory incision than to wait for time to clear up the doubtful points. Sarcoma of the femur, being in the majority of cases of the small round-celled variety, of periosteal origin, is one of the most malignant forms of tumor known. One cannot impress too strongly the importance of a very early diagnosis. In making an exploratory incision, one must not lose sight of the fact that this step involves a risk to which attention has seldom been called. I can but believe that cutting into a soft, highly vascular periosteal sarcoma, when removing a small portion for microscopical examination, occasionally permits detached fragments of the tumor, or, rather, infected sarcomatous cells, to be carried through the circulation to other parts of the body, causing early metastases. In cases in which the diagnosis cannot be cleared up without an exploratory incision, this risk of course must be taken. Mixter's tumor punch is of great service in these cases.

Prognosis.—Gross found that in 90 cases of sarcoma of the long bones, observed sufficiently long after operation, 26.6 per cent. were well over three years after operation. His statistics also prove the fact, already referred to, that the giant-celled sarcomata are less malignant, the percentage of cures in this variety being double that obtained in the other varieties.

Masse (*Archiv für klinische Chirurgie*, Bd. 39, S. 886) found 22 per cent. of cures in 39 cases collected from von Bergmann's clinic. My own statistics, including 15 personal cases and 9 cases collected from the records of the New York Hospital, show that 5 cases were well from two to nine years after operation. Of the 15 cases personally observed 10 were of the femur, 4 of the tibia, 1 of the fibula. None of these cases has remained well long enough to be classed as cures. The fibula case died of metastases in the lung two years after operation. Four other cases died within a year after amputation, and 7 cases were not traced.

Treatment.—Until recently there has been by no means a unanimous opinion as to the advantage of removing a portion or the entire femur for sarcoma; yet a study of the results of the earlier cases reported by Butlin and Gross, together with the results of pathological investigations showing that not infrequently in sarcoma of the lower end of the femur the disease has extended to the head of the bone, must convince us of the wisdom of amputation at the hip-joint, removing the entire bone in all cases. Even this extensive operation will probably save but a small proportion of the cases, on account of the tendency to early metastases, which not infrequently have already occurred but are not recognizable when the operation is performed.

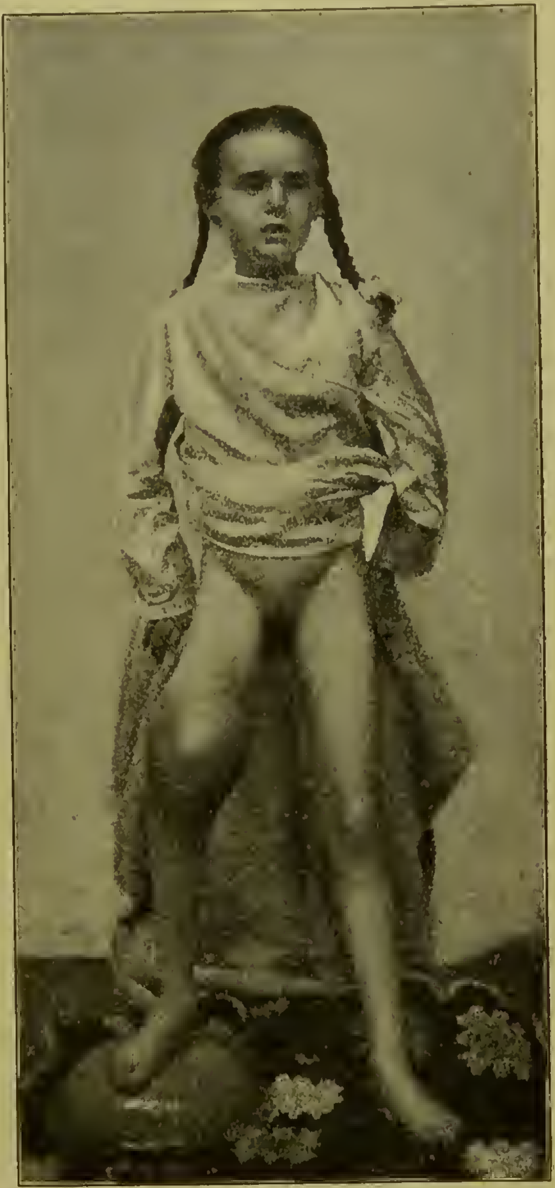

FIG. 13.—Periosteal Sarcoma of the Femur in a Girl Aged Eleven Years. (Original.)

As regards the results of operation, I am able to give few data based on personal observations, as my cases are too recent. I have amputated at the hip-joint in four cases of sarcomata, three of the femur and one of the soft parts. All of these cases recovered satisfactorily from the operation; one remained well at the end of six months; the others are recent cases. Pilcher (*Annals of Surgery*, Vol. XX., p. 22) states that of 4 cases of sarcomata of the femur operated upon at the Methodist Episcopal Hospital 1 died of shock from operation (amputation through the middle of the femur). In the other 3 cases hip-joint amputation was performed. All recovered. Two patients died in a few months of abdominal and thoracic metastases, while 1 was well a year after operation.

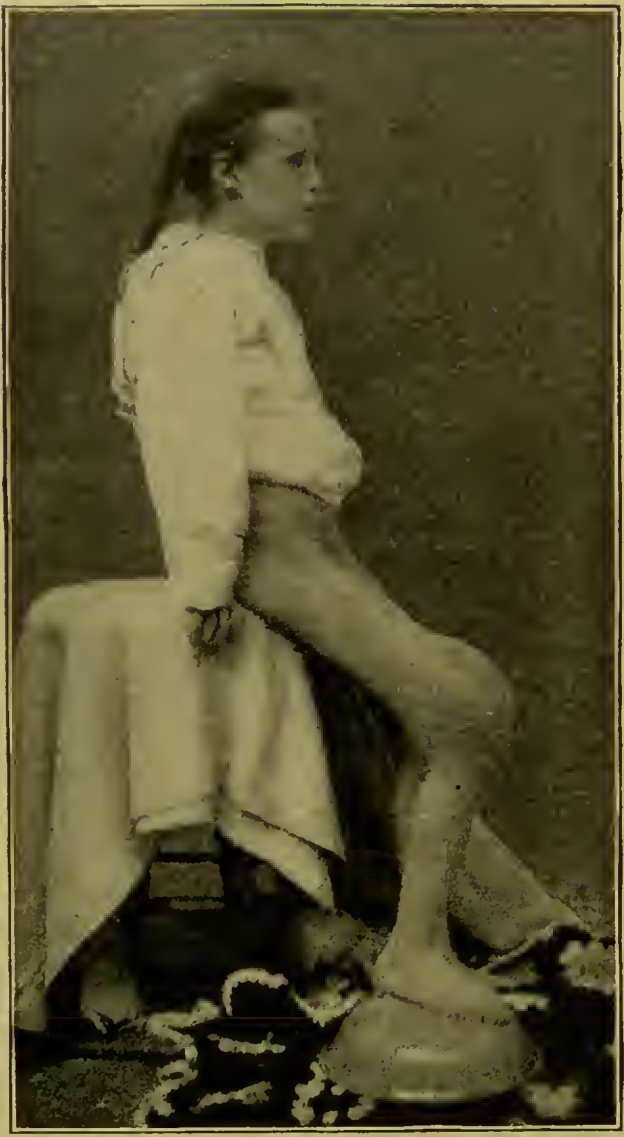

FIG. 14.—Sarcoma of the Femur; another view of the preceding case. (Original.)

Butlin (*loc. cit.*) states that the only treatment which would offer any hope of success is amputation as high up as possible above the disease, and as soon as the diagnosis can be made. In his later work ("Operative Surgery of Malignant Disease") he adds, "our present knowledge leads us to believe that amputations performed for this disease are very dangerous to life, and are rarely successful in affording a permanent cure or even a reasonably long relief from the disease." Of 36 cases which he collected only 2 of the patients were known to have been alive a year after operation. Nine, however, died directly from the effects of the operation. In one-third of the cases only, was amputation at the hip-joint performed, and in the remainder amputation of the thigh. Of the 8 cases of sarcoma of the femur observed by myself, hip-joint amputation was performed in 6. Two died within less than one year of internal metastases; 1 having also a larger recurrence in the soft parts of the stump and iliac fossa; one is well two years after operation; 1 was well when last seen seven months after operation. The other cases are recent. There was no mortality from the operation, which was performed in 3 cases by myself, in 2 by Dr. W. T. Bull, and in 1 by Dr. J. D. Rushmore. In one case only was amputation through the femur done, and death followed about four months later from lung metastases. In all of the cases that died of recurrence an exploratory incision was made prior to amputation, and to this fact it is possible to attribute the early generalization of the disease. In only one case was there a final cure effected.

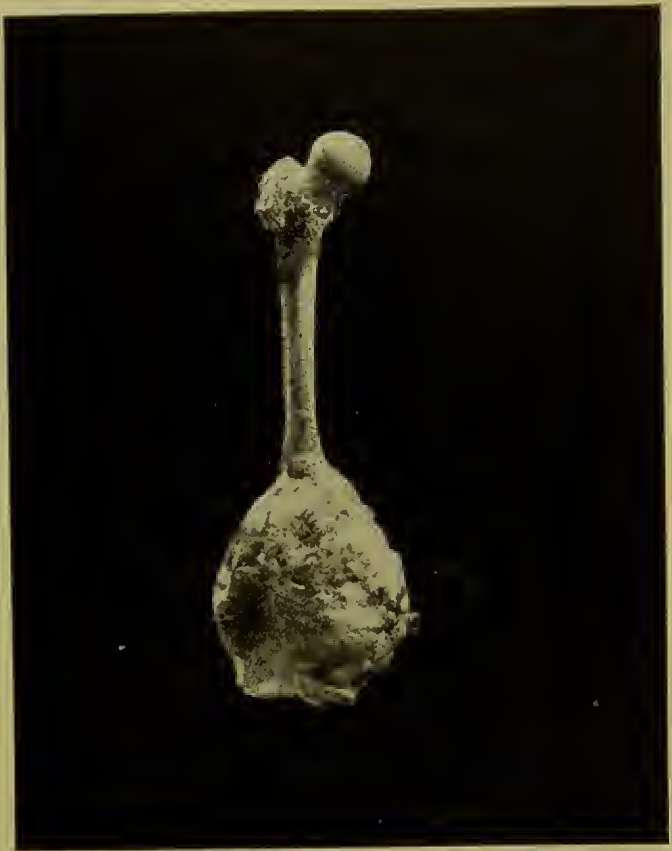

Fig. 15.—Spindle-celled Periosteal Sarcoma of the Femur in a Girl Aged Eleven Years, from preceding case. (Original.)

I believe that the prognosis in the collected cases of sarcoma of the femur would have been much better had they all been treated by removal of the entire bone. Amputation at the hip-joint at the present time is a far less serious operation than it was a few years ago, before the introduction of our modern methods for controlling hemorrhage. I have used Wyeth's method for the control of hemorrhage in hip-joint amputations—the use of steel pins with a rubber tube—in 4 cases with no mortality. The prognosis in tumors of the femur of central origin is considerably better.

SARCOMA OF THE TIBIA AND FIBULA.

This is almost always found in the upper end of the bone, and here again the origin may be either in the periosteum or in the central canal. Those of central origin are softer and not infrequently show pulsation. Sarcoma of the upper end of the tibia very frequently resembles an inflammatory swelling or one of tuberculous origin, and in all cases of doubt an exploratory incision should be made to render the diagnosis certain.

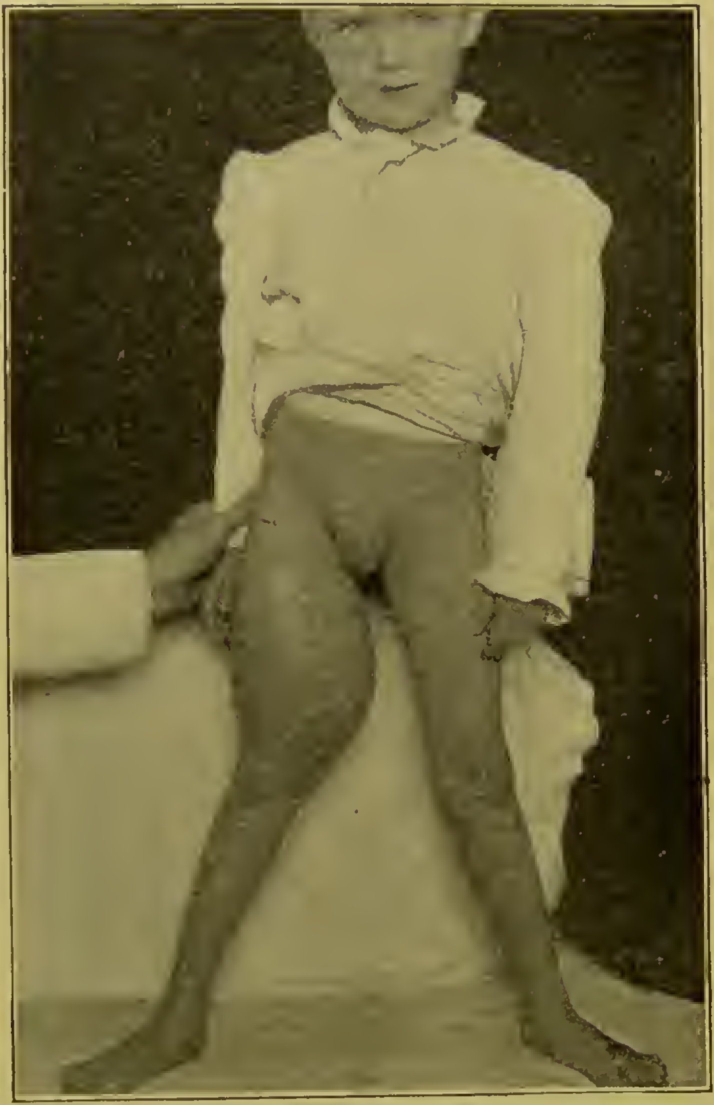

FIG. 16.—Periosteal Sarcoma of the Femur in a Boy Aged Six Years. (Original.)

Treatment.—The diagnosis of sarcoma having been confirmed, immediate amputation of the thigh should be performed. The prognosis is much better than in sarcoma of the femur, and the mortality is lower. Amputation through the lower thigh under modern aseptic principles ought to be attended with a mortality of less than ten per cent. I am aware that many surgeons, particularly Butlin, believe that in cases in which the disease is confined to the lower portions of the tibia or fibula it is safe to amputate below the knee. In view of the danger of the entire bone being infected, I think it better surgery always to amputate through the thigh (above the condyles).

As to the final results of sarcoma of the tibia and fibula, of 23 cases collected by Butlin 12 cases were lost sight of; 9 patients died within a few months after operation, and only 3 were known to be well from one to two years after operation.

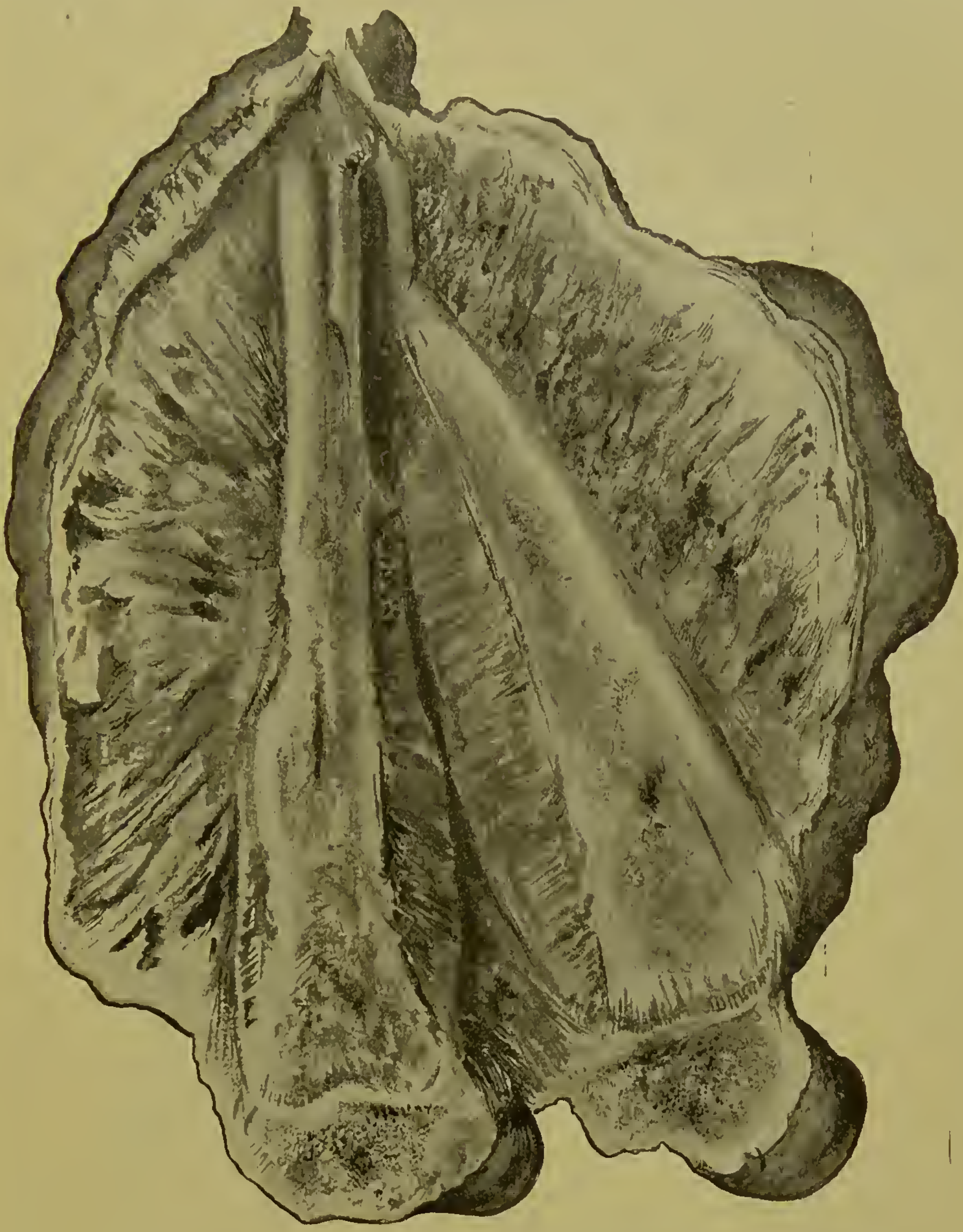

FIG. 17.—Periosteal Sarcoma of the Femur in a Boy Aged Six Years. (Original.)

The results of Dennis: "System of Surgery," Vol. IV., p. 80) are in striking contrast with the results collected by Butlin.

Dennis operated upon 20 cases of subperiosteal sarcoma of the long bones with but 1 death, due to shock from hip-joint amputation. Of the 20 cases all but 4 were traced. Of the remaining 16 cases there were but 3 deaths, and 13 patients were well beyond the three-year limit. It should be noted that Dennis strongly urges the removal of the entire bone in all cases of sarcoma of central or subperiosteal origin.

Lloyd (*Annals of Surgery*, 1898, p. 741) removed the entire fibula for sarcoma of the lower end, without amputation. This is said to be the first case in which the fibula was removed for malignant disease.

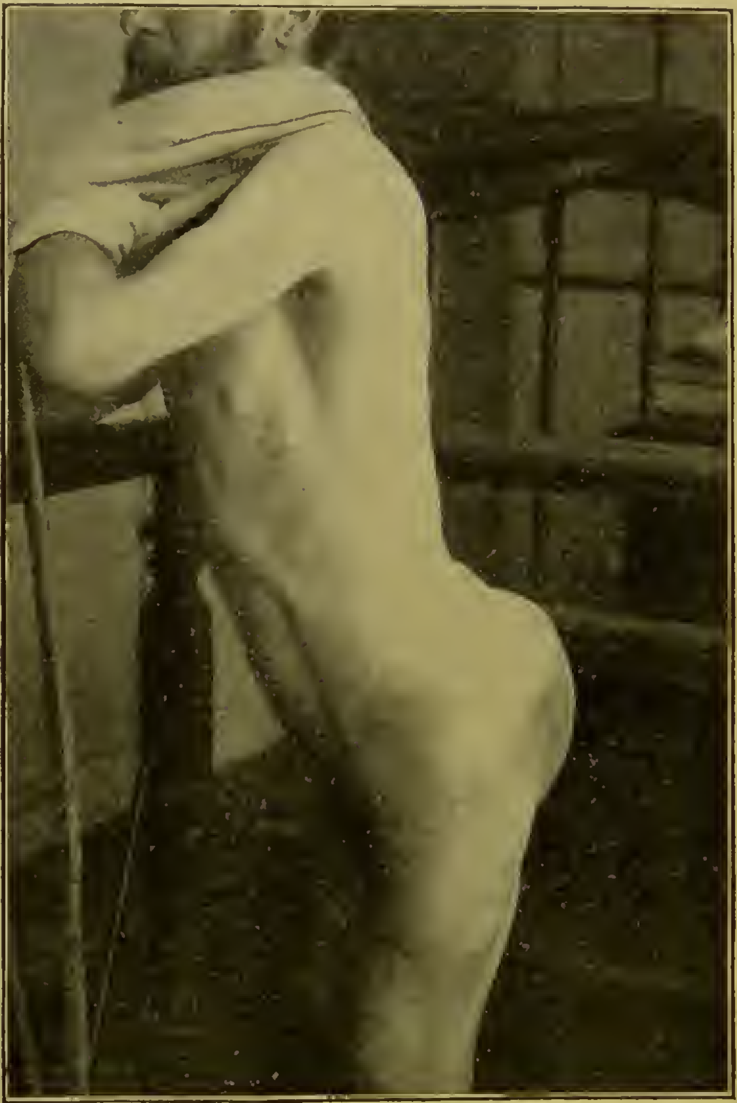

FIG. 18.—Charcot's Disease of the Hip Joint, Resembling Sarcoma. (Original.)

Two other cases have recently been reported, one by Bland Sutton (*British Medical Journal*, May 2d, 1896) and the other by Newman (*Glasgow Medical Journal*, 1896, Vol. XLVI., p. 137).

Lloyd's case is the more interesting from the fact that the patient was well at the time of the report three years after operation, and further from the fact that the mixed toxins of erysipelas and bacillus prodigiosus were used after the operation as a prophylactic measure. The report states that the adjacent surface of the tibia and the ankle-joint were slightly involved. It would appear that amputation of the thigh would be the operation of choice in such a case, and it is but fair to state that such was the operation advised by Lloyd but refused by the patient. The cure resulting from a more or less incomplete operation was doubtless due in some measure to the suppuration that occurred during the wound-healing as well as to the use of the mixed toxins. One case of round-celled myeloid sarcoma of the tibia was treated by the mixed toxins by J. E. Owens, of Chicago (*Journal of the American Medical Association*, August 27th, 1898), with the result of the entire disappearance of the tumor, the patient remaining well three years afterwards.

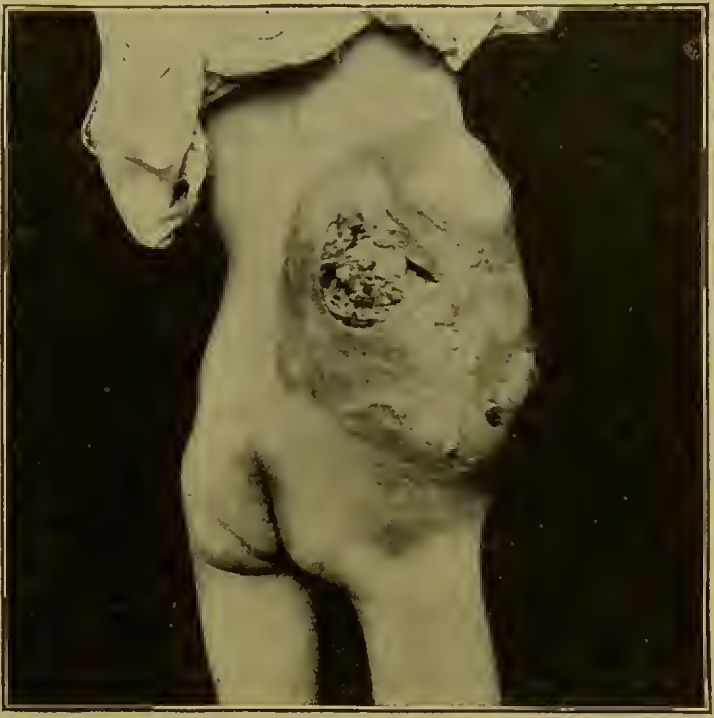

FIG. 19.—Chondrosarcoma of the Ilium. Recurrent after having once disappeared under the mixed toxins. (Original.)

SARCOMATA OF THE HUMERUS, RADIUS, AND ULNA.

These are occasionally seen, but are much less common than those of the femur, tibia, and fibula. In sarcoma of the humerus, the seat of the disease is most likely to be within the upper epiphysis of the bone, and it is usually of an extremely malignant type. In tumors of the ulna and radius—no matter what the type of sarcoma be—the upper extremity is almost always the one involved. Sarcomata of the ulna and radius, according to Butlin, are very much less malignant than those of the tibia and fibula.

Treatment.—Some authorities advocate resection of the diseased bone, but I do not believe this a safe procedure. Amputation above the elbow should be the operation of choice. As to *prognosis* little is known. Butlin was able to collect but three cases. Of these, 2 died of metastases, although amputation of the arm was performed. In the other case, a sarcoma of the radius, resection was followed by local recurrence, and amputation of the arm was later performed.

Sarcomata of the Short Bones.

Sarcomata of the metacarpal and metatarsal bones and of the phalanges are exceedingly rare. Butlin was able to find but one case of sarcoma of the metacarpal bone. It gradually commenced to grow six months after a violent blow with a piece of iron on the back of the hand. The forefinger and metacarpal bone were entirely removed, but the patient was lost sight of after recovering from the operation. The only other sarcoma of the metacarpal bone that I have been able to find is a case which I reported in the *Annals of Surgery* in 1891.

In this case also the disease developed after a blow, although it appeared immediately after the injury and continued to increase in size rather rapidly. The patient was a girl, eighteen years of age, in perfect health. The injury was received in the early part of July, 1890. The hand became a little swollen and somewhat painful the first night after the injury. The next few days the pain became a trifle less and the swelling, though somewhat diminished, did not disappear. A week later it increased slowly in size, the pain becoming more and more severe. A physician was consulted at the time of the injury, which was regarded as an ordinary bruise and was treated in the regular way. On August 12th, the pain and swelling having continued, the patient again sought medical advice, and the hand was immobilized by a palmar splint. During the month of September the pain and swelling both gradually increased. I first saw the patient on October 1st, two and a half months after the injury. Careful examination showed a small fusiform swelling just over the middle of the fifth metacarpal bone. The skin over this was perfectly normal; there was slight local heat; the swelling gave an indistinct sense of fluctuation on deep pressure. Pressure was very painful. The tumor was regarded by myself, as well as by other surgeons who saw it, as a subacute periostitis. Incision having failed to show any marked evidence of inflammatory trouble, on the 3d of November a portion of the tumor tissue was removed and examined microscopically. It proved to be a round-celled alveolar sarcoma. Two days later I amputated at the middle of the forearm. No enlarged glands at that time could be detected in the axilla. The patient's general condition was perfect. During the wound-healing there was no appreciable loss of flesh, no fever, and yet the pulse rate continued abnormally high—100 to 110—a fact which had been noted prior to the operation. The appetite gradually failed, and three weeks after the operation there was a severe attack of abdominal pain, localized in the epigastrium, lasting two or three days. A small area of resistance developed in this region, and there was marked tenderness on pressure. On December 11th, four and a half weeks after the amputation, a nodule the size of a small almond was discovered in the upper portion of the right breast. This was very tender and painful. The other breast, as well as both axillæ, were carefully examined, but nothing was found. The following day the nodule had perceptibly increased in size, and two smaller ones had appeared in the other breast. About the same time severe neuralgic pains developed in the left thigh. The patient's strength failed rapidly, and there was almost complete anorexia. On January 1st, less than two months after the amputation, jaundice appeared, and there was marked evidence of involvement of the liver and abdominal organs. The patient rapidly failed, and died on the 23d of January, about six months after the beginning of the disease.

SARCOMA OF THE PHALANGES.

While phalangeal sarcoma is very rare it occurs more frequently than metacarpal or metatarsal sarcoma. Six years ago, I operated upon one case of sarcoma of the second phalanx of the little finger in a woman aged forty-five years, removing the finger together with the metacarpal bone. The growth was about the size of an English walnut, and of four months' duration. It proved to be a giant-celled sarcoma of central origin. The patient remains alive and well at the present time, six years later.

Although the central tumors are situated in the majority of cases nearer the joint, it is very rare for sarcoma of any variety actually to involve the joint itself. This is a very important point in differentiating sarcoma from tuberculous disease.

SARCOMA OF THE CLAVICLE.

This is very rare. Butlin was able to collect but 3 cases. Resection was performed in all cases. One case (Mott's) was cured. I have personally observed 1 case of small round-celled sarcoma of the clavicle following fracture a year before. The patient came to me for a recurrence after operation, resection having been performed a few months previously. The disease involved the scapula and adjacent tissues so extensively that it was deemed inoperable. The mixed toxins were tried for a few weeks without improvement. An operation was then performed by Dr. W. W. Keen, who removed the remainder of the clavicle, the entire scapula, and the upper extremity. Although the patient recovered from the operation he died of recurrence about eight months later.

Sarcoma of the Breast.

Mr. Marmaduke Shield, of London, in his book on diseases of the breast, defines sarcomata of the breast as tumors taking their origin from connective tissue and characterized by a tendency to grow progressively and locally, and he states at the outset that there is no class of tumors more difficult to write of accurately and intelligently than sarcomata of the breast. It must be conceded that there are cases in which it is not always easy, even microscopically, to distinguish an alveolar sarcoma of the breast from carcinoma. There are certain other varieties of tumors not infrequently found in the breast that closely resemble sarcoma. Many tumors have been classed by the pathologists as fibroadenomata, yet the clinical history and rapid growth make it almost certain that they were sarcomata.

Another point in differentiating sarcoma from fibroadenoma is found in the fact that sarcoma is almost always of softer consistence. Fibroadenomata, while lacking the characteristic hardness of carcinomata, are still decidedly firmer and harder than the majority of sarcomata. Mobility is another distinctive feature to which Shield gives considerable weight. Sarcoma, while encapulated and somewhat movable, is not so freely movable as a fibroadenoma.

Still another point, which the majority of writers are prone to overlook, may be found in a careful record of the temperature. This point is noted by Shield, and is one which I have already mentioned at some length elsewhere in connection with sarcoma in general. Sarcoma of the breast, like sarcoma in other regions, if the growth of the tumor be rapid, nearly always gives rise to slight elevation in temperature, which would not be the case were the tumor benign.

Sarcoma of the breast is a rarer form of tumor than either adenoma or fibroadenoma. Bryant reports but 4 sarcomata in 100 cases of breast tumors observed by him. Inasmuch as in the older reports distinction is but imperfectly drawn between sarcoma and adenomatous growths of a mixed character, we are obliged to rely chiefly on recent statistics in forming an estimate of the comparative frequency of sarcoma of the breast. Gross collected 156 cases of sarcoma of the breast, and his tables show that the majority occurred between the ages of thirty and forty years. Bryant and Shield, however, believe that the disease less frequently attacks the breasts of younger women. It is more frequently found after the age of twenty-five. Of my own cases (six in number) none was under thirty, 3 were between thirty and thirty-five, and 3 were over thirty-five. Of 12 cases collected from the records of St. George's Hospital by Shield, 4 were between the ages of thirty and forty, and 6 between the ages of forty and fifty. In 14 cases collected from the Museum of the Royal College of Surgeons of England, 3 occurred under the age of thirty years, 3 between thirty and fifty, and 8 between the ages of fifty and sixty. From 60 cases collected by Shield, at the Middlesex Hospital, from 1875 to 1895, 15 were observed under the age of forty, 14 between the ages of forty and fifty, and 17 in subjects older than fifty years.

As regards the frequency of the various types of sarcoma, it may be mentioned that, in 17 specimens examined by the Royal College of Surgeons, 7 were spindle-celled, 4 were mixed (round and spindle), and 6 myxosarcoma.

Gross' statistics, based upon 156 cases of sarcoma of the female breast, show the spindle-celled type in 68 per cent., the round-celled in 27 per cent., and myeloid in 5 per cent. In many of the older statistics, the sarcoma is simply given as cystic. It should be borne in mind that this is really no distinctive type of tumor, inasmuch as cystic degeneration is exceedingly common in all types of sarcoma of the breast. In some cases this degeneration takes form in large cysts, from which clear straw-colored fluid can be extracted by an aspirating needle. In other cases the fluid is of dark brown or chocolate color. In some it is thick and glairy, due to mucoid changes. To these cases the term myxosarcoma is frequently applied. The old term, medullary or encephaloid cancer, should find no place in modern works upon malignant disease. There is little doubt that the tumors designated by these names by the older writers were rapidly growing sarcomata. Not infrequently sarcoma of the breast is so soft that it gives the appearance of fluctuation when no fluid is present. Melanotic tumors never occur in the breast proper, although they may originate in the skin over the breast, and secondarily involve the gland itself. I have observed three such cases.

Symptoms.—The clinical history and physical signs of sarcoma of the breast in the majority of cases are fairly typical. In a large proportion of the cases the disease has developed after an injury of some sort. When first noticed there is a small movable tumor, usually softer than the ordinary carcinoma, almost always encapsulated, and showing no tendency to infiltrate the surrounding tissue. As the tumor increases in size, the skin does not become attached, although in extensive growths it becomes very much thinned, and, on account of the dilatation of the cutaneous veins, may assume a pinkish or bluish color, which can seldom be mistaken for the changes that occur in carcinoma. The tumor has a more or less characteristic shape as it increases in size, tending to become protuberant. These tuberosities of varying size project from the central mass, and these are likely to differ materially in size and consistence. Should ulceration occur—a result which is by no means infrequent in highly vascular and rapidly growing round-celled sarcomata—fungoid granulations or, more strictly speaking, masses of tumor tissue may grow out from the ulcerated area. It is exceedingly difficult to keep such surfaces aseptic, and, on account of their high vascularity, severe hemorrhages are likely to occur. In one of my own cases (the size and appearance of the growth are well shown in Fig. 20), hemorrhages were frequent and excessive. In such cases the diagnosis presents little difculty. It is only the more slowly growing sarcomata that are likely to be confounded with other tumors. An important point in differentiating these growths from fibroadenomata is the early age at which the latter tumors develop, they seldom being found after the age of thirty, whereas sarcoma occurs most frequently after that age. In one of my own cases, the clinical diagnosis of probable sarcoma was made in a child aged eleven years. There was a history of injury preceding the development of the tumor, and physical examination of the tumor itself pointed strongly towards sarcoma. The fact that the disease is extremely rare in a child so young, combined with the fact that there were some enlarged glands in the axilla, made it impossible to rule out tuberculous disease. Microscopical examination of the tumor, when removed, showed it to be tuberculous, and not sarcomatous.

Treatment and Prognosis.—As soon as the probable diagnosis of sarcoma of the breast has been made, there is only one form of treatment to be considered, and that is speedy and complete removal of the breast and the underlying fascia, together with all the axillary glands. The technique of the operation does not differ from that of the operation for carcinoma, for although in sarcoma of the breast the axillary glands are not as a rule involved, recurrence not infrequently has taken place in the glands which the disease may already have involved without having given any evidence which could be obtained by palpation. The tendency to recur locally is very great, and spindle-celled sarcomata are said to be especially liable to local recurrence. Shield cites a case in which the patient died from exhaustion, at the age of forty-eight years. She had been under treatment for nineteen years, and had had nine recurrences. One of my own cases, one of angiosarcoma of the breast, in a woman aged fifty-nine years, had a very similar history: Seventeen years prior to the time when she came under my observation, there appeared, following a blow, a small tumor in her left breast. The first operation was performed fourteen years ago. The breast was removed, and no enlarged glands were present in the axilla. She remained free from recurrence for seven years, when the tumor recurred, grew slowly for two years until it had reached the size of an egg. The second operation was performed in May, 1889. Two years later, local recurrence again followed. No further operations were performed up to the time when she came under my care, on January 20th, 1895. There was then present a large tumor, occupying the entire region of the left breast, extending from the anterior axillary line to the sternum, and from just below the clavicle nearly to the upper border of the ribs. The tumor was fairly well fixed to the chest wall, was markedly protuberant, made up of more or less distinct nodules, the surface of which was purple in color, and in several places there was considerable ulceration with foul discharge. The tumor was unquestionably beyond operation. The patient's general condition was so extremely weak that she was scarcely able to walk alone. She was treated in the wards of the New York Cancer Hospital until September, 1895, at first with small doses of erysipelas and prodigiosus serum, and later with the mixed toxins. The tumor had become so much smaller that it was easily removable by operation. Her general condition had likewise much improved. Under ether the mass was removed. The periosteum of the ribs was not involved, but, as the skin over the tumor was thoroughly diseased, an area four by six inches was left to heal by granulation. Treatment was discontinued. The ulcer cicatrized rapidly. The patient left the hospital on December 14th, apparently well.

Unfortunately, I have been unable to trace the subsequent history of this case more than a few months after the patient's leaving the hospital. Microscopical examination by Prof. T. M. Prudden, of the College of Physicians and Surgeons, showed it to be a round-celled angiosarcoma.

A still more remarkable case cited by Shield was reported to the Bristol Medico-Chirurgical Society in 1778: The patient, aged forty-five years, was operated upon for primary spindle-celled sarcoma, and nearly died of hemorrhage at the first operation. A number of operations were subsequently performed, but she lived until the age of seventy-four, finally dying of extensive recurrence.

These cases plainly demonstrate the remarkable latency of the disease and the importance of performing a most complete operation in attacking the primary growth. These local recurrences, even when taking place ten years after the removal of the original tumor, are undoubtedly due to the leaving behind of infected cells, although of course too minute to be recognized by the naked eye. It has been found by a careful microscopical examination of the muscular tissues surrounding sarcoma of the soft parts that infected cells often pass for considerable distances beyond the substance of the tumor, finding their way not only along the fascia, but even between the bundles of muscle fibres themselves.

Therefore, with the idea in view of curing the patient of the disease, it were far better did we lose sight of the old idea that sarcoma is an encapsulated tumor which can be easily removed or shelled out, and operate on lines similar to the complete operation for carcinoma, removing the tissues wide of the original growth. If we follow such a method, I am convinced that the prognosis of sarcoma of the breast will show improvement as striking as has already been obtained in carcinoma of the breast.

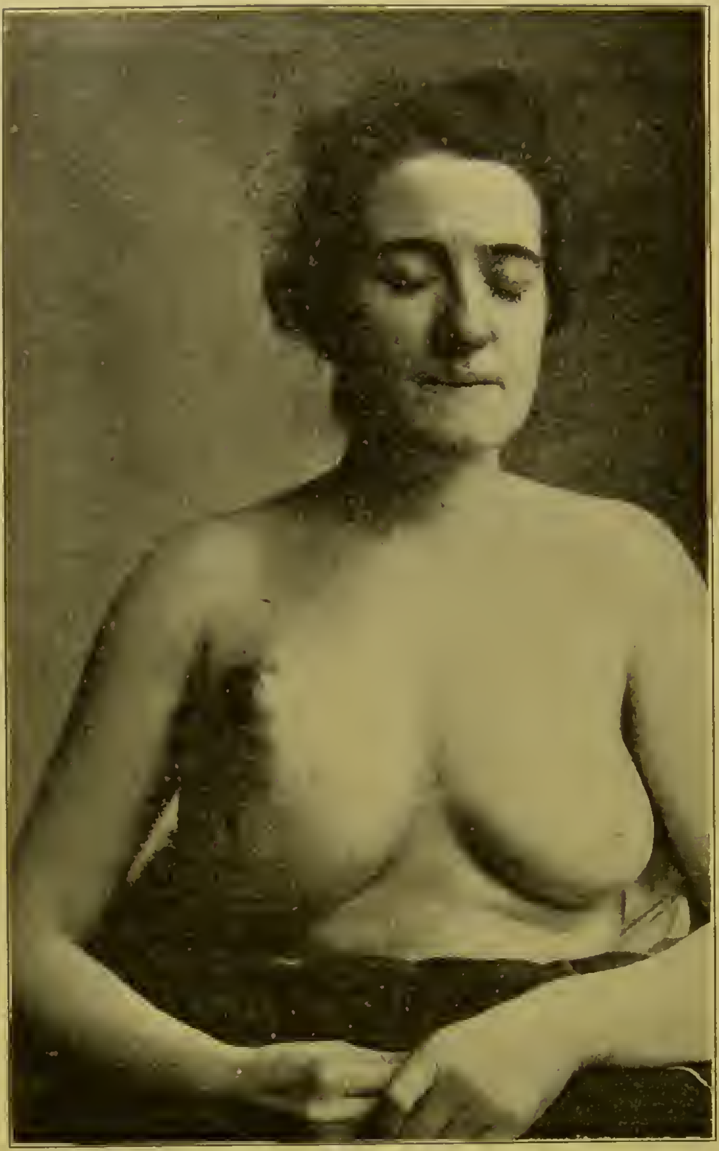

Fig. 20.—Sarcoma of the Breast. (Original.)

Sarcoma of the Breast.—M. M——, female, aged 31 years, unmarried, with good family history, struck her breast against an iron bracket while acting as clerk in a dry-goods store. She noticed a swelling immediately after the injury, and this continued to increase in size. Five months later the tumor was removed by operation, recurrence quickly following; four months from the first a second operation was performed. The patient died eighteen months after the injury from a supposed recurrence in the brain, five operations having been performed in the mean time. This case was operated upon by Dr. B. Gallaudet and Dr. William

T. Bull; it was not seen personally by myself. It is of interest, as it has an important bearing on the following case.

Sarcoma of the Breast.—A. M——, female, aged 31 years, a sister of the preceding. The patient had always been in perfect health until August, 1896, when she received a blow upon the right breast.

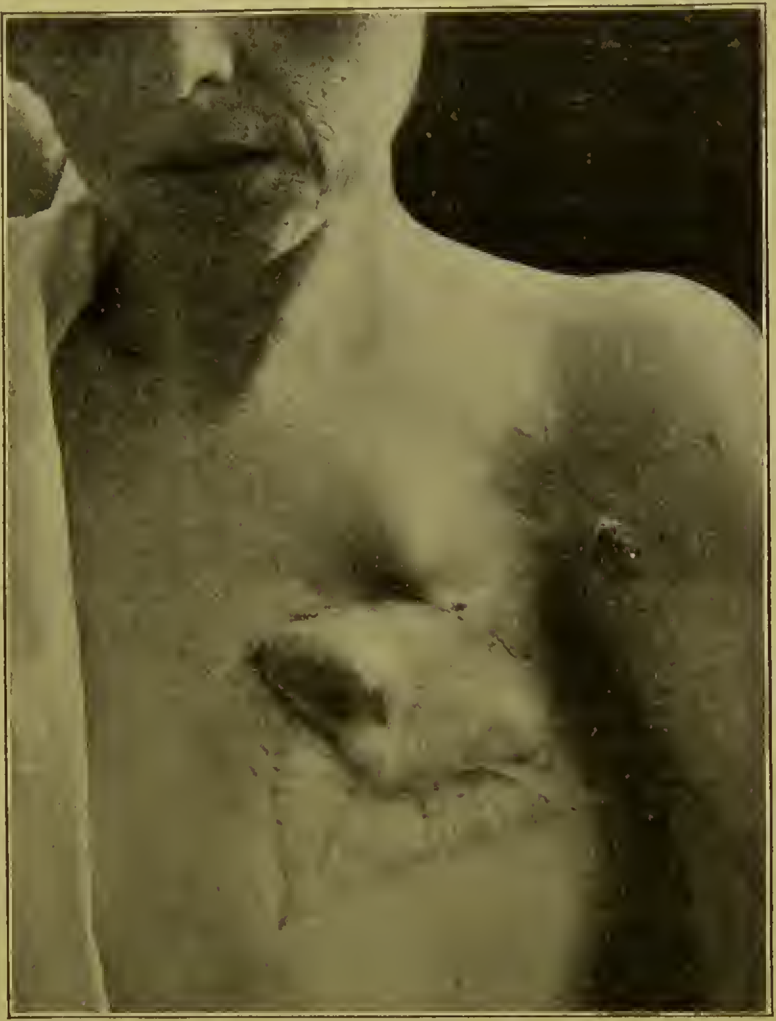

Fig. 21.—Sarcoma of the Breast (Round-celled), Recurrent. (Original.)

A few days afterwards she noticed a lump at exactly the site of the injury. This grew rapidly, but it was not painful until November. In December, 1896, it became exceedingly painful and was growing with great rapidity. The patient consulted a physician, who advised internal treatment. On February 8th, 1897, I saw her in consultation with Dr. William T. Bull. At this time the entire right breast was occupied by a spheroidal tumor, about the size of a large cocoanut, markedly protuberant, slightly fixed to the chest wall, not involving the axillary glands. The skin was thin and glossy, and of a deep purple color over the most protuberant parts (see Fig. 20). The tumor grew with enormous rapidity and soon began to slough. The patient died of exhaustion in April, 1897, or seven months after receipt of the injury. It is of interest to note that in these two sisters the sarcoma developed immediately after an injury in both cases, the tumor occupied the right breast in both instances, and both were just thirty-one years of age at the time when the tumor developed.

Sarcoma of the Testis.

Both sarcoma and carcinoma occur in the testis, but sarcoma is by far the most common. I have seen but one case of carcinoma of the testis, while I have observed eight of sarcoma. Several cases are described by Mr. Butlin in his book on sarcoma and carcinoma, and I quite agree with him in his statement that, if a large number of sarcomata or carcinomata were compared, it would be found that the characteristics which they possess in common are more numerous than those by which they are distinguished. There is very little difference in regard to cause, rapidity of growth, amount of pain, or physical characteristics, such as shape, size, and consistence. The clinical features are so much the same, that the microscope must usually be employed in order to differentiate the two. The age of the patient, as well as a previous history of trauma, often enables one to make a probable diagnosis of sarcoma, inasmuch as carcinoma seldom occurs in patients under the age of thirty-five, and the history of trauma is not so likely to be present. In nearly all of my cases of sarcoma of the testis there has been a history of antecedent trauma. I have recently observed several cases in which the relationship is quite striking.

Round-Celled Sarcoma of the Testis Following Bicycle Injury.—G. S——, male, aged 29 years, with good family history, always perfectly healthy, received an injury to the left testicle from a bicycle fall in August, 1896. A swelling appeared in the testis in September, and increased rapidly in size. The first operation was performed in June, 1897, by Dr. Millbank, of Albany. Speedy recurrence in the cord and inguinal glands followed. Four operations were performed, two by myself. The erysipelas toxins were tried for three or four weeks without effect. The tumors recurred and the patient died in January, 1898.

Round-Celled Sarcoma of the Testis Following Bicycle Injury.—E. K——, male, aged 22 years, with good family history; previously in perfect health. On attempting to learn to ride a bicycle, July 1st, 1896, he fell and injured the left testis. Within one week after he noticed an increase in size; the increase continued, but the growth was not painful. In August, 1896, it had reached the size of a fist. In May, 1897, the patient was operated upon and the tumor was removed. Recurrence followed in May. A second operation was performed in June, 1897. There quickly followed abdominal recurrence; the patient lost flesh and strength very rapidly, and died early in October, 1897. Autopsy showed nearly all the abdominal organs extensively involved. After generalization had occurred the erysipelas toxins were tried for ten days with little effect; only very small doses could be borne.

Sarcoma of the Testis Following Injury.—The patient, 27 years of age, was a farmer by occupation. Family history good. Personal history: Always well until two years ago, when he was kicked in the testicle by a horse. A small lump appeared immediately, and, although the lump never disappeared, it did not increase in size until four months ago, when the patient fell through a hay rack, again injuring himself in the same region. Immediately afterwards, the old swelling of the testis began to increase in size, and continued to do so rapidly until up to the present time. Physical examination on August 8th, 1898, showed the right testicle to be the size of a cocoanut. A portion of the tumor was solid, and the upper portion showed distinct fluctuation, as if there were fluid in the cavity of the tunica vaginalis; general health perfect. A diagnosis of sarcoma was made and immediate castration was advised. An incision was made over the inguinal canal, just as in Bassini's operation for inguinal hernia, and the entire testis with overlying tunica vaginalis and four inches of the cord were removed *en masse.* The wound healed by primary union.

Diagnosis.—Butlin states that carcinoma of the testis is most frequent between the ages of thirty-five and forty. He was able to collect forty-one cases of sarcoma, and from a study of these cases he found that the disease was most frequent at two periods of life; the first from birth to the age of ten, and the second from thirty to forty years, the latter period corresponding very nearly to the period within which carcinoma is most frequently found. Most of the cases were round-celled sarcoma; but, curiously enough, the cases of spindle-celled sarcoma nearly all occurred in patients under ten years of age. As Butlin has pointed out, the secondary enlargement of the glands in sarcoma of the testis is contrary to the general law which holds goods for sarcoma, namely, that infection seldom occurs through the lymphatic glands. In nearly all the cases of sarcoma of the testis which have come under my care, the secondary involvement did take place through the lymphatics, and occurred usually in the retroperitoneal glands. Clinically, it is entirely unnecessary to attempt to differentiate sarcoma from carcinoma, but there are certain varieties of benign tumor which it is important to differentiate.

A pure cartilaginous tumor or enchondroma of the testis is exceedingly rare, and this fact, together with the uniform hardness of the tumor, makes it easier to distinguish it from the malignant tumors of a mixed nature, in which cartilage occurs together with sarcomatous tissue.

The most difficult condition to distinguish from malignant disease is *tuberculosis* of the testis. A careful clinical history, in which a physical examination is made not only of the testis but of the chest and abdomen, should always be procured. If the disease is tuberculous, in a very large number evidence of tuberculous lesions will be found elsewhere. A physical examination of the testis itself should alone, in nearly every case, make the diagnosis clear. In most cases of tuberculous testis the development of the tumor has been more gradual than in malignant disease. Many of the cases will give a history of six months or a year or two years, with no or very slight pain; the patient's attention is first called to a hard lump situated almost always in the epididymis. This lump, if seen in the early stages, will be found to have a peculiar hardness, quite characteristic of tuberculous disease. It is more nodular than a malignant tumor; if it has existed for some time, we shall find the skin adherent and still later reddened as well as adherent, which condition, after a longer or shorter time, ends in ulceration of characteristic appearance. Before the stage of ulceration there is not infrequently more or less fluid in the tunica vaginalis, and the cord is apt to be thickened and harder than normal. Examination by the rectum in a considerable proportion of the cases will show enlarged seminal vesicles.

If the disease be malignant, the history of the case will be somewhat as follows: If the disease has not reached an advanced stage, the patient will appear in perfect health. There will be nothing about him to arouse even a suspicion of tuberculous disease. In a great majority of cases there will be a history of injury at some longer or shorter interval prior to the development of the tumor. The tumor will probably have existed but a few months, perhaps only a few weeks. Examination will show that it involves not only the epididymis, but the testis itself. The tumor has a smooth, symmetrical outline, has a very solid, heavy feeling, the veins of the scrotum will be found dilated, fluid may or may not be present in the tunica vaginalis—more frequently not. The patient will probably complain of pain, although too much reliance should not be placed upon this symptom, and the skin will be found perfectly movable. The consistence of the tumor is usually firm, but quite distinct from the characteristic hardness of tuberculous disease. The majority of cases being round-celled sarcomata, the consistence is uniform, while in the mixed tumors, in which some cartilage is present, the consistence varies in different places.

Gummata or syphilitic tumors may occasionally be mistaken for malignant tumors, but the history of antecedent syphilis, and the slow increase in size will render the diagnosis easy. Malignant disease of the testis, whether it be sarcoma or carcinoma, is such a grave matter that no chances whatever should be taken by regarding it as a possibly benign tumor and waiting for the development of events. If any error is to be made, it should be always on the side of having removed a benign tumor of the testis rather than having allowed a malignant tumor to wait for time to assist in the diagnosis. Castration should be performed in every case, and the earlier the better. Curling, in his admirable book on diseases of the testis, advises us to "exhibit mercury, so as to make the gums slightly sore, in order to make a diagnosis between chronic orchitis and the early stages of malignant disease." This advice I believe to be bad, for two reasons: the one being, as I have already pointed out, that not infrequently cases of actual malignant disease do show striking temporary improvement under vigorous antisyphilitic treatment; and the second is that, if no improvement whatever is shown, and the disease is finally recognized to be malignant, most valuable time has been lost, and the chances of cure from operation have been markedly lessened. I agree most heartily with Mr. Butlin, who says: "For my own part, I would sooner risk an incision into an inflamed testis—incision made with all due care—than delay the castration of a malignant tumor." Butlin further states that the exact diagnosis is not in every instance a matter of importance. The diagnosis between an innocent and a malignant tumor is of little consequence, provided the disease be clearly recognized to be a tumor, for the treatment is the same in either case.

Prognosis.—As regards prognosis, we must admit that it is exceedingly bad. Of my own 8 cases, not a single one has remained well sufficiently long to be regarded as cured. Of 56 cases collected by Butlin, in patients whose age varied from a few months to upwards of seventy years, 4 died of causes directly due to the operation. Of 52 persons who survived the operation, 21 died later of recurrence, and only 8 were known to be alive and well some months after castration. One, a case of spindle-celled sarcoma, was well two years after operation. Another was well three years after castration, which had been performed within three months of the first appearance of the tumor. All of the children died of recurrence within a comparatively brief period. In cases in which the patient finally died of the disease, there was a respite of several months and in some instances years of freedom, which sufficiently justified the operation.

Treatment.—There is no question as to the advisability of operative interference. The only thing to be emphasized is the importance of early diagnosis, and, in cases in which this is impossible, an exploratory operation with castration, if necessary.

One point I should like to mention in connection with the technique of the operation: In two cases which have come under my personal observation, recurrence took place in the stump of the cord, which had remained behind after the primary operation. I believe it to be a very important addition to the technique to make the incision, as in the case I described, parallel to Poupart's ligament, opening up the aponeurosis of the external oblique quite as freely and in the same manner as in the Bassini operation for inguinal hernia, making it possible to remove the cord well beyond the internal inguinal ring. This procedure I have carried out in two recent cases.

Sarcoma of the Kidney.

This subject has already been briefly treated of in Volume I. of this series by Mr. Reginald Harrison, but it is one of increasing importance, and will be referred to again here for the sake of uniformity. Our knowledge of the pathology of renal growths has been much increased by the just published work of Mr. T. N. Kelynack, of Manchester, on "Renal Growths." He has endeavored to collect all of the cases of renal tumors thus far reported, and his carefully compiled bibliography, covering thirty pages, will prove of great value to any one who desires to make a thorough study of malignant disease of the kidney.

The old and imperfect methods of classification of tumors of the kidney are rapidly giving place to more scientific methods, and though we are still in the transition period, much progress has already been attained. It is to be hoped that the increase in interest in this class of growths, and their acknowledged surgical importance, will result in sufficient clinical knowledge to render an early diagnosis possible, and enable us to effect a cure. As Kelynack says: "The modern spirit of research demands that clinical deduction shall as far as possible be based upon pathological facts. Hence a diagnosis of renal 'tumor' will not now suffice."

None of the malignant forms of renal tumor, until very recently, was called "cancer," but very often "encephaloid growth" or "fungus hæmatodes." This fact shows that the study of these tumors must be begun anew, and practically the old reports of cases are of little avail for scientific treatment.

Inasmuch as all forms of malignant disease of the kidneys have been grouped under the general term "cancer," it is not possible to carefully differentiate the clinical symptoms and physical signs, though this will be attempted as far as possible.

Bland Sutton in 1893 states: "It is impossible to write an account of carcinoma of the kidney until surgeons are more alive to the interest of the question and take steps to place malignant tumors of the kidney, while fresh, in the hands of experienced pathological histologists." And this criticism still holds good, though to a less degree.

Frequency.—Malignant growths of the kidney are comparatively rare. Ebstein found but 3 cases of carcinoma of the kidney in 8,300 cases of carcinoma. Virchow states that only 0.5 per cent. of malignant neoplasms occur in the kidney. Kelynack has carefully searched the pathological records of the Manchester Royal Infirmary and has found but 9 cases of primary renal growth, which gives a proportion of 0.19 per cent. of cases dying from various causes.

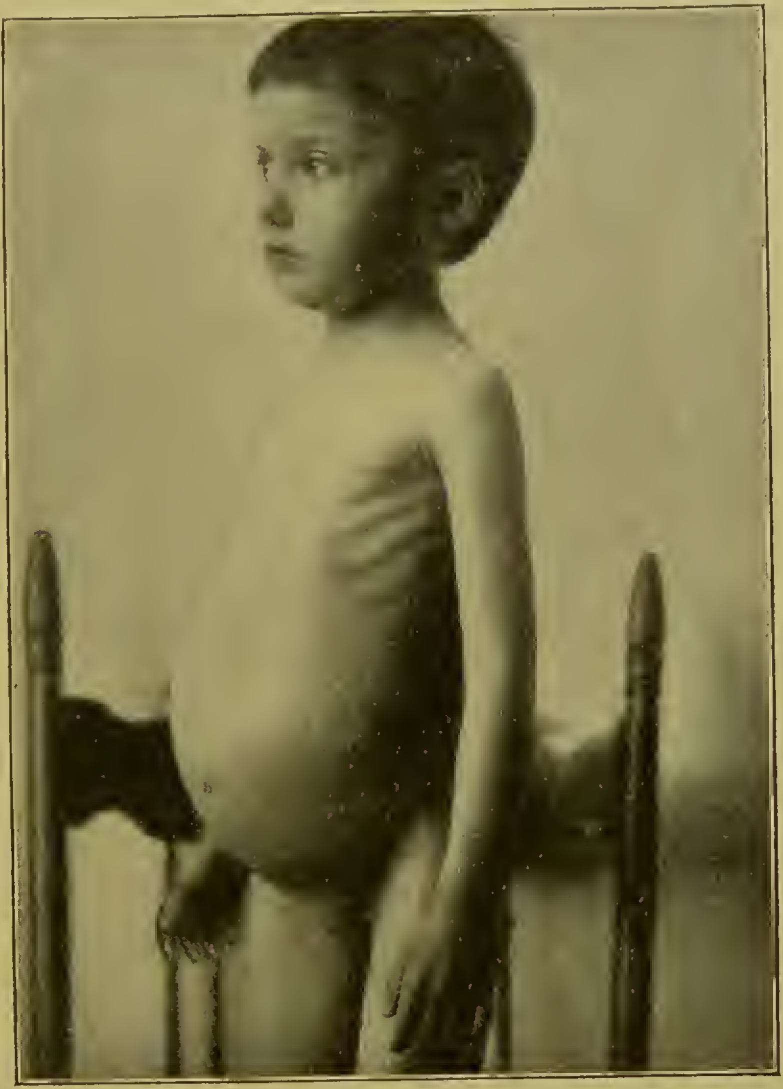

FIG. 22.—Sarcoma of the Kidney in a Girl Aged Five Years. Recurred after abdominal nephrectomy.

Kelynack believes that from two to three per cent. is a fair estimate of the proportion of malignant growths of the kidney to malignant disease in all other parts of the body.

Sarcoma of the kidney is undoubtedly more common than carcinoma, though the opposite opinion was held not long since. The diagnosis is, however, in many cases attended with the greatest difficulty, for the reason that malignant adenomatous growths often simulate sarcomata very closely.

Of 306 cases of all ages and both sexes collected by Kelynack 115 were sarcomata, 22 myosarcomata, 142 carcinomata, 15 fibromata or lipomata or mixed, and 12 adenomata.

Many of the cases grouped under "carcinomata" were reported as "cancers" but were undoubtedly sarcomata.

Age.—About 50 per cent. of the cases of sarcoma of the kidney occur in children under the age of ten years; 74 out of 160 cases collected by Kelynack were under five years of age. The disease may even occur in the fœtal kidney, as shown by Jacobi.

General Symptomatology of Malignant Disease of the Kidney.—A *tumor* is the most important physical sign, and is one that is present at some period of the disease in most cases. It is usually found early. It is, especially in children, the first sign of the disease in more than one-half of the cases, and in adults in about one-fourth. Guion found enlargement in 129 of 133 cases, and Roberts in 61 out of 64 cases.

Careful bimanual palpation should be employed, and in some doubtful cases it may be wise to examine the patient under ether.

The tumor is situated usually in the space between the border of the ribs and the crest of the ilium. It varies greatly in size, being as a rule larger in children than in adults. The largest tumor of the kidney reported thus far weighed thirty-six pounds. The outline is usually symmetrical, and the enlargement extends laterally rather than upwards or downwards. The contour of the abdomen and the position of its contents should always be noted. The shape of the tumor often corresponds to the shape of the kidney or is frequently spheroidal.

The position with reference to the bowels is important. The colon may almost invariably be found overlying the tumor, and herein lies an important distinction from tumors of the liver or spleen.

The consistence of the tumor is apt to vary; cystic degeneration is often present, and this gives the sense of fluctuation which is so often found in renal sarcomata. In carcinoma this is much less frequent.

Hæmaturia is an important sign, but one which is found in only one-half of the cases. It may appear at any period of the disease and in a few cases has been the first sign noted. The amount of blood lost varies greatly. The urine may be of a deep blood color or only slightly tinged. In some cases the microscope only shows the presence of blood.

In the two cases in which I have personally made frequent examinations of the urine, some blood could always be found by microscopical examination, but occasionally there would be a large increase in the blood sufficient to color the urine.

In melanotic sarcoma of the kidney (a very rare condition) the urine has been found of very dark color, due to the pigment of the new growth. The quantity of urine is about normal until the later stages of the disease, when it is diminished. The specific gravity has always been low in the specimens I have examined.

Guion and others have called attention to *varicocele* as a symptom of renal tumor. This would be of little significance if on the left side, where varicocele may be said to be almost a normal condition; but if found on the right side with a history of sudden development, it may be of some value. Various other symptoms may arise from pressure of the tumor.

In large growths the liver is pushed up so that the thoracic organs have less space and freedom. Adhesions may occur between the growth and any of the abdominal viscera.

In children, in whom the growth is usually very rapid and the tumor is often of large size before the surgeon sees the case, the diagnosis is easy. The abdomen is greatly enlarged and presents a peculiar appearance that is strongly suggestive of renal tumor. The veins of the abdominal wall are distended. The solid or semi-solid tumor, which is easily outlined by palpation, occupies the region of the kidney. The bowels are pushed towards or beyond the middle line, except the colon, which is nearly always in front of the tumor but may be so empty that it is dull on percussion. The position of the child on standing is very characteristic, leaning backwards like a woman in advanced pregnancy, in order properly to fix the centre of gravity.

In the early stages of the disease the general health appears normal, but as the growth becomes large, emaciation occurs. In my own cases in children there was marked loss of flesh when first observed.

Ascites and œdema of the lower extremities may occur, but are not common.

Diagnosis.—Treves has said that "renal tumors are among the most difficult of abdominal enlargements to diagnose correctly," but until we are able to make a correct diagnosis during the early stage of the disease we cannot hope for better results from surgical interference. We must distinguish (1) tumors of the kidney from tumors originating in the neighborhood of the kidney, and (2) benign from malignant tumors.

Omental and mesenteric tumors may simulate renal tumors, but the location and general outline, as well as the increased mobility in most cases, will make a correct diagnosis possible. These tumors seldom have the smooth outline and spheroidal shape of the kidney tumors, being more flattened and irregular. They are much more readily moved about.

Cystic kidney sometimes may be mistaken for a renal tumor. Cystic disease of the kidney, however, is frequently bilateral. This, together with the general symptoms of the disease, makes it possible to differentiate the two conditions.

Tuberculosis may be mistaken for a malignant tumor, and in some cases the diagnosis can be made only with a microscope. In cases of doubt, careful examination should be made of the lungs for signs of tuberculosis, as the disease is seldom primary in the kidneys. Kelynack found that in cases when tuberculous lesions were found in the kidney, such lesions were present elsewhere in the body in ninety per cent. of the cases, and the lungs presented evidence of either latent or active tuberculosis in seventy per cent., while the bladder was involved in seventy-five per cent.

Hydronephrosis or pyonephrosis very often closely resembles malignant disease of the kidneys. Careful examination of the urine, combined with the clinical history of the case and bimanual examination of the tumor, will in most cases settle the diagnosis. Should there still be doubt, no harm is likely to result from exploratory puncture with a fine aspiration needle.

Perinephritic abscesses have also been mistaken for renal tumors. Here again an exploratory incision or aspiration may be required. I have seen one case in a child, aged two years, in which a large swelling in the region of the kidney was at first thought to be a cystic sarcoma. It had developed rapidly, was situated in the exact location of the kidney, was about the size of two fists, bulging forwards into the abdominal cavity and posteriorly through the muscles so as to simulate a lumbar hernia. The child had fallen some months before, which fact still further increased the suspicion of sarcoma. Careful examination, however, showed the growth to be too fluctuating for a sarcoma, and the diagnosis of hydronephrosis was regarded as the most probable. A needle was introduced and pure pus withdrawn. Examination of the urine was negative, thus ruling out hydronephrosis and pyonephrosis. An exploratory incision was made, and about a quart of cheesy tuberculous pus was evacuated; and the finger introduced into the cavity showed the condition to be tuberculous disease of the vertebræ.

This is an exceedingly interesting case, from a diagnostic point of view. It shows the necessity of our using all the means at our command in making a diagnosis. There are various other conditions that have occasionally been mistaken for renal tumor; among these may be mentioned dilated bladder, hydatid cyst, irregular enlargements of the liver, distended gall-bladder, enlargements of the spleen, ovarian tumors, and even pregnancy. In not a few cases sarcoma of the kidney has been mistaken for ovarian tumor.

The diagnosis between malignant and non-malignant tumors of the kidney can almost always be readily made, in view of the great rapidity of growth in the malignant tumors.

Treatment.—Until very recently, the let-alone policy of treatment has been almost universally adopted. Many of the leading surgical authorities, even of recent date, look upon nephrectomy for malignant disease with doubt and disfavor. Thornton, as late as 1889, speaking of renal sarcomata in children, said that "removal is commonly followed by such speedy recurrence that an operation is barely justifiable"; and he believes that, if the operation is successful, the speedy recurrence which follows is likely to cause far more suffering than if the disease had been allowed to take its natural course.

Still later, Bland Sutton said that "nephrectomy for renal sarcoma in children is absolutely unavailing, and is fast falling into disfavor."

Very many authorities are cited by Kelynack to show the gradual veering of surgical opinion in favor of early nephrectomy for malignant disease, whether it occurs in the young or the old. American surgeons, one of whom was the first to perform nephrectomy for renal tumor, have been largely responsible for this change of opinion.

The successes of Abbe have proven that some of the most unfavorable cases may not only survive operation, but may remain permanently cured. One of Dr. Abbe's cases was perfectly well upwards of four years after operation. Among recent opinions as to the advisability of operation may be quoted that of Osler, of Baltimore, who says: "A very large proportion of the cases comes first under the care of the physician, whose province it is to recognize the condition; and, to do justice to his patient, he should be thoroughly familiar with the advances which have been made in the development of renal surgery."

Careful examination of all of the cases of malignant disease in which operation has been performed and a study of the final results justify us in concluding that, while the prognosis is still extremely bad—and this is especially true in the younger patients—operation should be advised in all cases in which there is a reasonable probability that the entire tumor can be removed. In performing nephrectomy for malignant disease, every portion of the fibrous capsule should be removed and a careful search should be made for enlarged glands, which, if found, should be scrupulously removed.

At the present time the mortality from the operation is not far from fifty per cent.; but there is no question that, with earlier diagnosis, this mortality could be reduced, and the final results will probably show a corresponding improvement. Before operation, careful examination should always be made of the other kidney, as well as for secondary deposits. Aside from operation, no other form of treatment offers any hope even of temporary relief. Various remedies have been used—for example, iodide of potassium, Chian turpentine, erysipelas toxins—but thus far little has been accomplished. Snow recommends cocaine and antipyrin, and advises against the use of opium in these growths. Fortunately, the pain is not as a rule severe, but in those cases in which an anodyne is required, one should feel no hesitation in using morphine.

Sarcoma of the Upper Jaw.

According to Senn, malignant tumors of the jaws are for the most part sarcomata. The statistics, however, of these tumors do not bear out this statement. The most complete investigations on cancer of the upper jaw are embodied in the paper of Max Martens (*Deutsche Zeitschrift für Chirurgie*, Bd. 44, p. 483). The author collected all of the cases of cancer of the jaw treated at the Surgical Clinic at Göttingen from October, 1875, to October, 1895—86 in number. In 74 of these cases there was a total resection of the upper jaw, and in 12 a partial resection. Of the 86 cases 57 were carcinomata, 27 sarcomata. The relative proportion of the two diseases varies little from that shown in the statistics of Weber (133 cases). Gerth collected 125 cases of carcinoma, 96 of sarcoma; Küster, 20 of carcinoma, 14 of sarcoma.

Nearly all types of sarcoma are found in this locality, although the majority are round-celled. In Martens' collection of cases, all of the carcinoma patients were over forty years of age, and the disease was considerably more frequent in men than in women, the proportion being 34 to 23. In the case of sarcoma 50 of the patients were over forty years of age, only 12 under.

The *clinical history* and *symptomatology* of these cases may be very briefly described: Without any known cause the patient may notice a bulging in the region of the antrum, or, in some cases, a slight fulness in the roof of the mouth. In some cases of sarcoma the disease apparently begins in the alveolar process of the jaw, the first symptom being irritation at the root of a tooth, and later on the tooth becomes so loose that it is easily pulled out. The attention of the dentist may be called to a slight softening of the alveolar process, and a tendency to bleeding. The course of these cases is generally rapid, and in a short time the signs which at first simulated inflammatory disease become characteristic of malignant tumor.

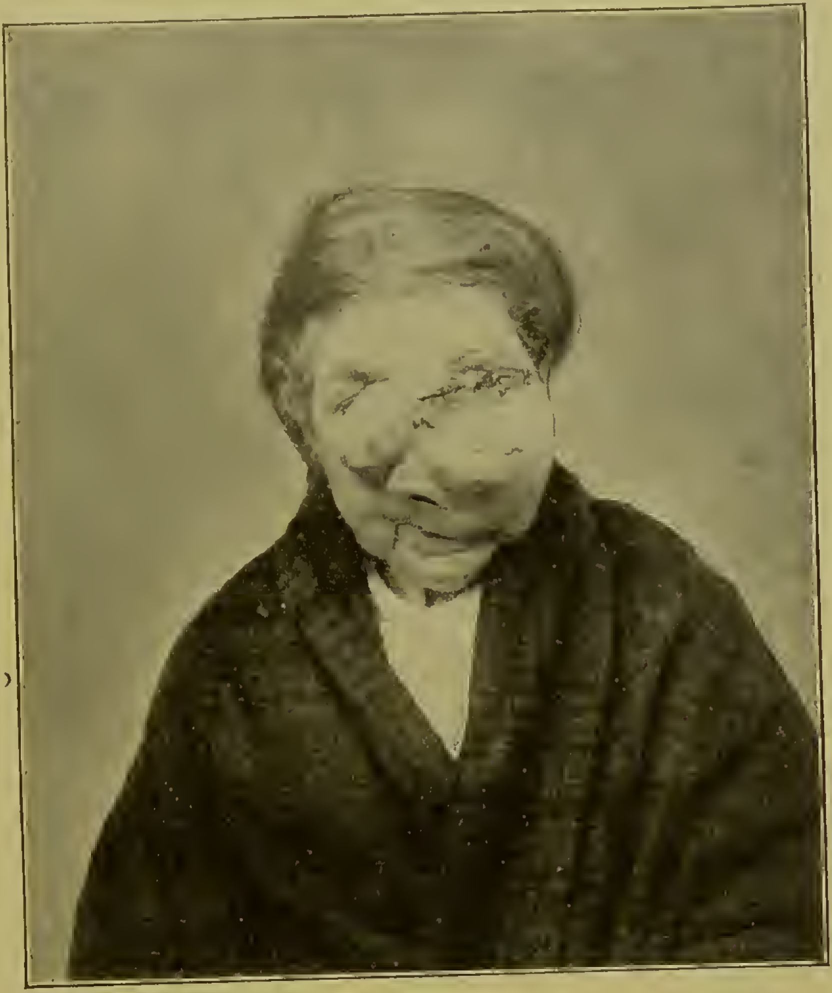

FIG. 23.—Malignant Adenoma in a Woman Aged Eighty Years. (Original).

In many cases the disease, starting in the antrum, extends to the orbit, and in addition to the bulging of the antrum there is apt to be some exophthalmus. In most cases no glandular enlargements are to be found, although occasionally the cervical glands are affected.

Treatment and Prognosis.—No other procedure than excision of the jaw, partial or complete, is to be considered. If the diagnosis be made sufficiently early, and the bone be excised wide of the tumor, there is a reasonable hope of permanent cure. The mortality, however, from the operation is considerable. In Trendelenburg's cases: 14 total excisions, there was a mortality of 28 per cent. Martens collected the statistics of 14 leading operators, between 1843 and 1870—124 cases in number—of which 44 died, giving a mortality of 35.5 per cent. Butlin collected 108, with a mortality of 30 per cent. Of the 74 cases of total resection at the Göttingen Clinic there were 22 deaths, or a mortality of 30 per cent. In the partial resections the mortality was only 8.3 per cent. The most frequent cause of death, so far as known, was bronchitis or pneumonia following the operation. Meningitis occasionally follows the operation, and this possibility should always be considered.

As throwing much needed light upon the question of final results in operation for cancer of the upper jaw Martens' cases are of very great value. Of the 74 total resections, 33 died of the operation; 33 later of recurrence. Of the 12 partial resections, there was but 1 death from the operation, while 6 died of recurrence.

The prognosis is somewhat better in sarcoma than in carcinoma. Out of 26 cases of carcinoma 76 per cent. died of recurrence, and of 13 cases of sarcoma, 62 per cent.

In regard to the duration of the cases that were classed as cured, there were 8 cases of carcinoma well beyond five years, 6 of which were well from nine to eighteen years. Of the cases of sarcoma, 5 remained well from six to thirteen years, 6 after three years.

In regard to the best method of operating, many different incisions have been proposed; probably the best is that known as Weber's incision, in which the upper lip is divided at the main line as far as the septum of the nose; then the incision is carried below the nostril on the affected side, around the base of the nose, up the side, nearly to the inner canthus of the eye. It is then extended by a convex incision along the edge of the orbital floor, nearly to the external angle of the eye. The contents of the orbital cavity should be carefully separated from the floor with a periosteal elevator. The malar bone can be divided, either with a chain saw, or, better still, a Gigli wire saw, or a chisel. The nasal process should then be divided with bone forceps. The section at the junction of the maxillary bone can also be easily made with the Gigli wire saw. By means of a lion-tooth forceps, and the judicious use of heavy, blunt-pointed scissors, the bone can now be easily removed.

The *after-treatment* is of considerable importance. The patient should be kept in a prone position for several days. The mouth should be most carefully and frequently cleansed with some strong antiseptic wash. The gauze packing may be removed in two or three days.

Sarcoma of the Lower Jaw.

Primary malignant tumor of the lower jaw is nearly always sarcomatous. Epithelial disease starting in the neighboring tissues may secondarily involve the jaw. Many of the cystic tumors of the lower jaw have been regarded by some authorities as epithelioma. Sarcoma of the lower jaw may be of either central or periosteal origin; clinically the chief point of distinction is rapidity of growth. Central tumors develop more slowly than the periosteal and may be several years before reaching any considerable size. They are almost always found in the sides or anterior portion of the jaw, rarely originating in the ascending ramus. In periosteal tumors the growth is often so rapid that the trouble is at first regarded as inflammatory. I have recently seen a case in which a very large tumor developed in a few weeks and the disease ran its entire course in less than six months. In the early stage it could not be differentiated from inflammatory trouble. The above illustration shows very well the appearance of a periosteal sarcoma starting in the alveolar process of the anterior portion of the lower jaw removed from a man seventy-two years of age. No attempt was made in this case to preserve the continuity of the bone. Resection was easily performed by means of the Gigli wire saws. The patient made a good recovery, although there was considerable suppuration about the ends of the divided bone.

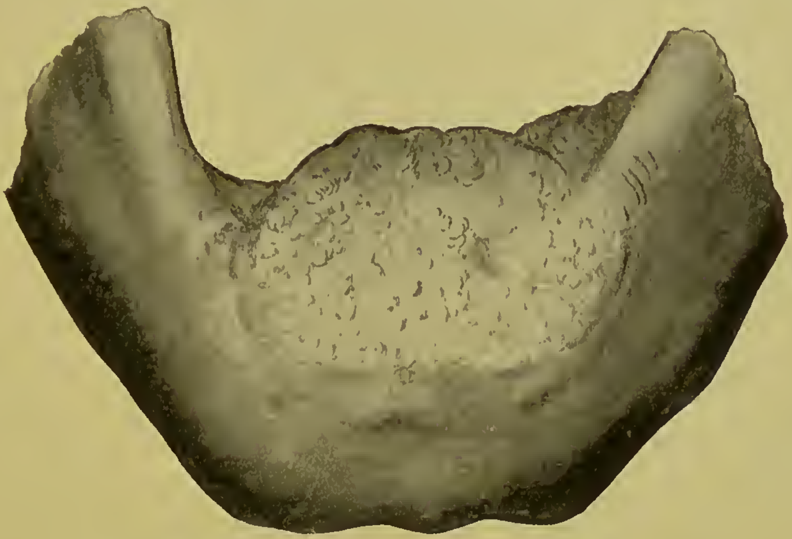

FIG. 24.—Round-celled Sarcoma of the Lower Jaw. (Original.)

Treatment.—No treatment other than radical operation should be considered. If the tumor be of slow growth and central origin Butlin believes that the gouging or scraping out of the tumor will suffice. Partial resection I think the safer operation. This may be performed in some cases so as to leave a bridge of bone, thus preserving the continuity of the jaw. It is most important to remove the neighboring soft structures in sarcoma of periosteal origin, for these tumors are not, as a rule, encapsulated, tending rather to infiltrate the adjacent tissues. Metastases are extremely frequent in periosteal sarcoma of the jaw; the lymphatic glands in the immediate vicinity are rarely affected, although the glands in other portions of the body are frequently the site of secondary deposits.

Resection of the lower jaw is not a difficult operation; the soft parts are separated by means of the knife and periosteal elevator; a tooth may be removed at either end of the tumor in order to facilitate the sawing of the bone. If, however, the Gigli wire saws be used, removal of the tooth should seldom be necessary. If the disease involves a considerable portion of the anterior part of the jaw, it will be necessary to divide the tissues externally, including the lip. In rare cases it is necessary to remove one-half of the jaw. In performing this operation the external incision should always be made. Hemorrhage is, as a rule, easily controlled by temporary packing with iodoform gauze; subsequently the mouth should be frequently and carefully cleansed with some antiseptic solution. Butlin advocates the free use of powdered iodoform in these cases and believes that harm seldom results from this practice.

Results of Operation.—Butlin has collected 104 cases with 14 deaths, or a mortality of 14 per cent.; in 5 cases the deaths were due to exhaustion. In all of the fatal cases the entire half of the jaw had been removed. The majority of the operations were performed prior to 1880, hence the operation at the present time should have a mortality considerably below that shown by Butlin's statistics.

As regards the final results, in 19 cases of subperiosteal sarcoma, in which the operation consisted in resection of a portion of the bone containing the tumor, there was no mortality; 8 patients died of very rapid recurrence, 8 were lost sight of, and only 1 in the entire number was well at the end of two and a half years.

The final results in the cases of central sarcoma are much more satisfactory. Of 143 collected by Butlin, 8 died of the operation; 20 were lost sight of; 13 were reported well at from a few months to six years after operation, 6 cases having remained well more than two years, 4 more than three years. Of the 4 successful cases 2 were giant-celled, 1 spindle-celled, and 1 so-called "fibrofying" sarcoma.

Sarcoma of the Orbit.

While much has been written in text-books ot sarcoma of the eye, little reference can be found to sarcoma originating in the orbit itself or its periosteal covering.

A recent writer (Sattler, in the *Cleveland Medical Gazette*, 1897) has well said: "This cavity is a veritable stronghold for malignant disease, and when once invaded it may as well be considered as beyond the scope of successful surgical interference."

Of my two hundred cases sixteen were primary sarcomata of the orbit. The appearance of the tumor is well shown in Fig. 25. The disease is almost always round-celled and of an exceedingly malignant type, as shown by the following report of a case observed by me:

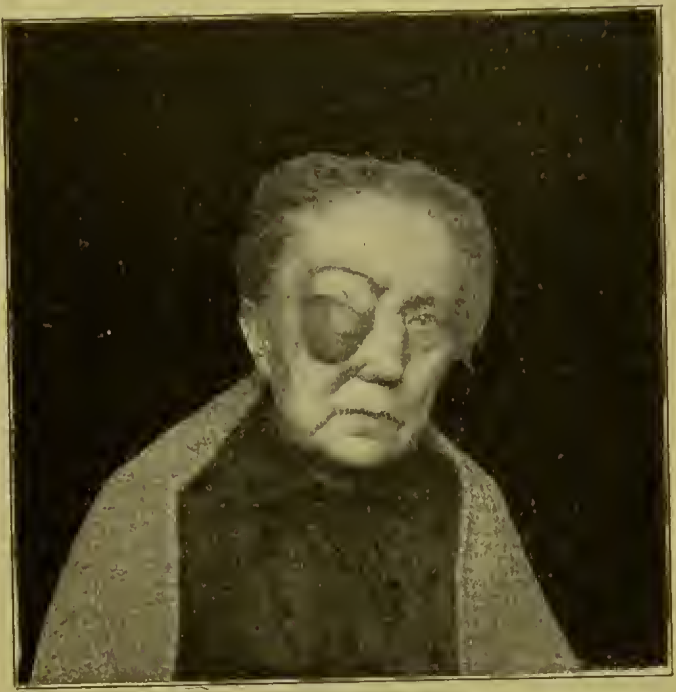

FIG. 25.—Sarcoma of the Orbit. (Original.)

Male, aged 30 years. Grandmother died of cancer of the stomach. He was always well until January, 1898, when he began to notice a "watering" of the right eye. Vision was perfect. Two or three weeks later he noticed an enlarged gland in the neck on the right side, and at the same time the eye began to bulge. My first examination, March 11th, 1898, showed very marked exophthalmus, with an enlarged gland, the size of an English walnut, in the submaxillary region. He was admitted to the Post-Graduate Hospital March 12th, 1898, and the mixed toxins of erysipelas and bacillus prodigiosus were used for three weeks. The disease showed no improvement, but there was little increase. The toxins were then given up, and the following week there was very marked increase in the size of the tumor. The eye projected so greatly and the pain was so severe that it was decided to enucleate it merely as a measure for giving relief. I removed the eye and at the same time the enlarged gland in the neck. The eye itself was in no way involved, but had been simply pushed out mechanically by the sarcoma which apparently originated in the subperiosteal region of the orbit and almost entirely filled the cavity.

Examination of the tumor, as well as of the gland from the neck, showed the structure of both to be "round-celled sarcoma of a highly vascular type."

The disease progressed very rapidly, extending into the brain and causing death May 14th, 1898, or five months from the first symptoms of the trouble.

The following case is an example of even greater malignancy. In this case it is not possible to tell whether the disease originated in the orbit or in the superior maxilla:

A boy, aged 5 years, with good family history, complained on October 1st, 1898, of pain on swallowing.

A swelling supposed to be an abscess was seen bulging downwards from the roof of the mouth. A few days later the eye began to bulge and became very painful. The exophthalmus increased rapidly. Three weeks after the beginning of the symptoms I saw the patient in consultation with Dr. Theodore Dunham. In this short time the disease had advanced to the following extent: The left eye was markedly protruding, the lids were red and œdematous; there was also some bulging of the superior maxilla, both externally and in the cavity of the mouth. The tumor involved the soft palate as well, and the child had the greatest difficulty in swallowing. When it is considered that this hopeless condition had developed in a healthy child in three weeks we appreciate the malignant character of the growth.

Diagnosis.—Little can be said of the diagnosis of sarcoma of the orbit. In most of the cases that have come under my observation pain was not a prominent symptom until the later stages of the disease, or until exophthalmus had appeared.

A most interesting case, as showing the difficulty in making a diagnosis in some cases, especially in the spindle-celled type, which is comparatively rare in the orbit, has just been referred to me by Dr. W. H. Carmalt, of New Haven:

The patient was a woman, aged 35 years, unmarried, with no family history of malignant disease. About eight years ago, having taken cold during menstruation, the flow suddenly stopped. The same day the right eye became suddenly swollen and protruded noticeably.

She consulted Dr. Carmalt, who believed a blood-vessel had become engorged and ruptured. The protrusion never subsided. In 1891 an operation was performed by Dr. Carmalt and the exophthalmus was found to be due to a fibro-sarcoma originating in the roof of the orbit. The eye was not removed. The disease recurred two years later, and grew very slowly until December, 1897, when the eye was removed and the orbital cavity carefully cleaned out. A second recurrence soon followed, and a third operation was performed October 4th, 1898.

Increase in Malignancy.—A very important feature in connection with this case was the fact that with the gradual increase in the malignancy of the tumor, as shown by the more rapid recurrence after each operation, there likewise appeared a change in the type of sarcoma. At the first operation the examination showed the growth to be a "fibrosarcoma"; at the second a "myxosarcoma," showing an increase in the cellular elements; and at the last operation the tumor removed showed the typical structure of a "round-celled" sarcoma. I am not aware that attention has been called to this fact of a gradual change in the type of sarcoma, yet it is supported by the histories of several other cases that I have observed. The following case of sarcoma of the abdominal wall is introduced here, as it strikingly illustrates this transformation:

The patient, a man aged 69 years, without anything in family or personal history worthy of note, first noticed a tumor in the right side of the abdominal wall in 1867. It grew slowly and was excised ten years later, or twenty years ago. It was pronounced a "fibrous tumor," but recurred five or six years later, having become four to five inches in diameter. A second recurrence followed two years later, and a third operation was performed. He remained well for about three years longer, when the disease again recurred. The history of operation and recurrence, with the intervals gradually becoming shorter, continued up to April 26th, 1897, when I first saw the patient. The last operation had been performed but six weeks before, yet two tumors had appeared in the mean time in the region of the old cicatrices. They were so soft as to be almost fluctuating, and were situated just under the fascia of the muscle. I removed them, and the microscopical examination showed them to be "pure, small round-celled sarcomata, very vascular." Speedy recurrence and death, a few months later, proved the high malignancy of the growth, which had become slowly changed from a fibrosarcoma of low malignancy to a round-celled one of very high malignancy.

Treatment.—As regards the treatment of orbital sarcoma I believe operation seldom if ever effects a cure, and if the disease is far advanced it should not be performed except to afford relief from pain and tension. The prognosis is absolutely bad. I have never known of a case of cure.

Sarcoma of the Ovaries.

Although malignant disease of the uterus is very common, it is rare to find either sarcoma or carcinoma originating in the ovaries. In a recent table of tumors of the ovaries, collected by Swan of the Johns Hopkins Hospital, comprising 1,388 cases operated upon by nine surgeons, there were but 137 solid tumors, and of these 19 were sarcomata and 22 carcinomata. Ovarian sarcomata are most common about the ages of puberty and of the menopause. Zangmeister, of Czerny's clinic, has made a very extensive study of sarcoma of the ovaries (*Bruns' Beiträge*, Bd. 16, S. 397, 1896). Thirty-three cases were collected from Czerny's clinic between the years 1880 and 1893. None of these patients was under twenty years of age; 9 were between twenty and thirty, 5 between thirty and forty, 14 between forty and fifty, 9 between fifty and sixty, 2 between sixty and seventy. According to Williams (*Lancet*, i., 1897) a large proportion of cases of malignant disease of the ovary occur in young girls, and of 12 cases collected by Adelbert, 6 occurred in girls between the ages of seven and nine years. The only case observed by myself occurred in a girl aged seven and one-half years. The following is a brief report of the case:

Mixed (Round and Spindle) Celled Sarcoma of the Ovary.—M. B——, a girl, aged 7½ years. Good family history. In September, 1894, she fell, striking hard upon the abdomen. A tumor in this region was noticed early in December, or about ten weeks after the injury. Operation was performed on December 27th, 1894, by Dr. J. B. Deaver, of Philadelphia. A tumor nearly as large as a child's head was removed, apparently originating in the left ovary. Seven months later there was a recurrence, and the tumor grew with great rapidity; a second operation was performed, with the result of a recurrence six months later. The patient was treated at the New York Cancer Hospital, in March, 1896, for three weeks with the toxins of erysipelas, with the result of a considerable decrease in the size of the tumor. In April, 1896, she developed typhoid fever, and died six weeks later.

Inasmuch as most of the lists of cases have been collected from special clinics of diseases of women (exclusive of children), it seems probable that the statistics do not give a fair proportion of children.

Twenty-six of the patients in Czerny's clinic had borne children, two were sterile, eleven were unmarried. As regards the causation, very little is known. Menstruation in some cases was normal in early life. In one case it had ceased since the thirteenth year. In two cases it was very profuse, and associated with spasmodic pain. In some patients menstruation was irregular; yet, on the other hand, in several cases it was perfectly normal. With one the disease began just at the conclusion of the menopause; in another in pregnancy; in still another, soon after childbirth.

Symptoms.—One of the earliest symptoms noticed in many patients was the feeling of a lump or swelling in the abdomen, pain being usually absent. In some cases frequent micturition and incontinence, or difficulty in passing urine, were among the first symptoms noticed. In a few cases gastric symptoms were first observed, such as loss of appetite, vomiting, or heartburn. In other words, the subjective symptoms of sarcoma of the ovaries were extremely varied and not at all characteristic. Pain in those cases in which it was a prominent feature of the trouble was usually localized in the lower abdomen, although sometimes it was referred to the lumbar region and, in a few cases, extended down the thighs. In some cases pigmentation of the skin, more especially about the nipple, the umbilicus, and the linea alba, was noticed. In some cases the disease was associated with ascites. Physical examination usually shows a hard, solid, or semi-solid tumor, situated to one side of the median line, of somewhat irregular outline, and generally moderately movable. In some cases the tumor may be felt by vaginal examination. The uterus will in most cases be found pushed to the opposite side. A very remarkable fact in connection with this disease is the frequency with which it is found on both sides. Statistics show that it occurs on the right side in 40 per cent. of the cases, on the left in 36.5 per cent., and on both sides in 23.5 per cent. The tumor seldom attains very large size, although the growth is in most cases very rapid. It is very frequently cystic in parts, either multilocular or unilocular, and the majority of cases are spindle-celled sarcoma.

Diagnosis.—The leading points of diagnosis are the presence in the abdomen in one or both sides of the uterus, of a spheroidal tumor, either wholly or in part solid in consistence, irregular in outline, fairly movable, with a history of rapid development. Ascites is often present, and in advanced stages of the disease there is usually cachexia. Metastases occur very early, and are frequently found in the liver or the lungs.

Treatment and Prognosis.—The treatment, of course, consists in operation performed as early as the diagnosis is made, unless the presence of metastases or the size of the tumor contraindicates operation.

In regard to the results of operation: Of Zangmeister's cases 7 died as a result of the operation, 2 from other causes; of the remainder, 3 died of metastases, 3 of recurrence; 12 patients were alive and entirely well a considerable number of years after operation. One died of diabetes sixteen years later. Most of the cases had gone upwards of three years without any evidence of return. Butlin ("Operative Surgery of Malignant Disease") states that the mortality of the operation in 99 cases that he collected with great labor was 33 or 33⅓ per cent., a far higher mortality than in simple cystic disease of the ovaries.

As regards the final cures of 55 cases reported from Schroeder's clinic 4 only were well beyond three years, 2 of which were sarcomata and 2 carcinomatous cysts. Of 47 cases collected by Butlin in which the after-history was known, only 5 were well beyond three years. As regards the relative malignancy of sarcoma and carcinoma of the ovary, little is definitely known. The prognosis is exceedingly grave in both.

Sarcoma of the Tongue.

This subject has been most exhaustively studied by Marion of Paris (*Revue de Chirurgie*, 1897, Nos. 3, 7, 8). He was able to find but 24 cases in literature; 12 were under thirty years of age, 3 between thirty and forty, 3 between forty and sixty, and 3 over sixty years of age.

Diagnosis.—There is no sign absolutely characteristic of sarcoma of the tongue. The characteristic that appears most worthy of note is rapid evolution. The tumor may be either intralingual or pedunculated. If in the substance of the tongue it gives the appearance of being an encapsulated rather than an adherent or infiltrating tumor. In some cases of the pedunculated or protuberant variety the surface may assume a mushroom appearance, but with little tendency to bleed. The differential diagnosis must be made from carcinoma, gumma, cysts of the tongue, lipoma, lymphadenoma, and actinomycosis.

Prognosis.—The prognosis of sarcoma of the tongue, treated according to modern methods, ought to be relatively good, as compared with cases of carcinoma of the tongue. Of the twenty-four cases collected by Marion, twelve, or fifty per cent., died after a comparatively brief course. In the other twelve a so-called "cure" followed, but further data in regard to the duration of the freedom from the disease are needed before we can estimate accurately the curability of the disease. The prognosis varies with the variety of sarcoma, being more favorable in the spindle-celled, and graver in the round-celled.

The reported cases show us the importance of further operating upon sarcoma of the tongue in the event of recurrence after the first operation. Several cases have been recorded in which a final cure resulted after three or more operations. Dr. Robert Abbe showed a patient before the New York Surgical Society who was well ten years after removal of the tongue for sarcoma.

Sarcoma of the Skin.

Sarcoma seldom originates in the skin, but three instances being found in my two hundred and seven cases.

In one case the disease began without known cause in the sacral region in a man aged forty-five. He did not know of its existence until a secondary tumor the size of a duck's egg appeared in the right groin.

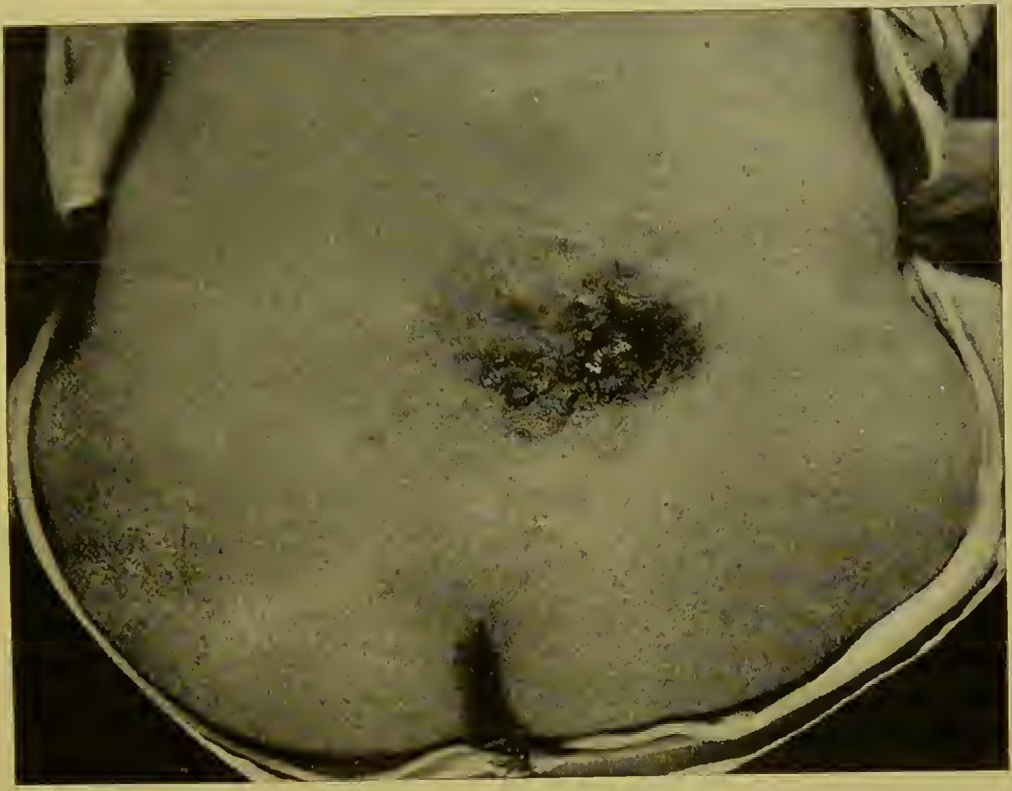

FIG. 26.—Primary Sarcoma of the Skin.

The tumor in the back was four by six inches in size and involved the entire thickness of skin and contained numerous tuberosities of varying size. The tumor was of a reddish-purple color and was not fixed to the underlying tissues. Microscopical examination showed it to be a mixed round, spindle, and oval celled sarcoma. The case has been reported at length in my early papers on the erysipelas toxins, having been treated successfully by living cultures and later by the toxins. The man remained well for three and a quarter years when the disease recurred in the abdomen and quickly proved fatal.

The second case was a round-celled sarcoma containing considerable pigment (melanotic).

A third case, recently observed, originated in the skin over the dorsal region of the left hand. Almost simultaneously a similar tumor appeared about the middle of the dorsal portion of the forearm. The growths were removed by Dr. W. O. Roberts, of Louisville. Local recurrence followed in the forearm a few months later, though its true nature was not recognized for some months, owing to the fact that a portion of tissue that looked most suspicious from the granulating portion of the unhealed wound was pronounced by two excellent pathologists as showing no evidence of sarcoma. The skin about the region was thickened and reddened, closely simulating a dermatitis following the use of bichloride of mercury. The wound healed quickly under the exhibition of mercury and the iodide of potassium, but the peculiar condition of the skin continued during the summer of 1898, though moderate doses of the mixed toxins were given as a prophylactic measure. In September, 1898, a portion of the skin was removed, as it seemed more suspicious, and examination showed it to be a round-celled sarcoma involving all the layers of the skin. Amputation of the arm was at once advised and performed by Dr. Roberts.

Sarcoma of the Lymphatic Glands.

When sarcoma originates in the lymphatic glands, it is one of the gravest diseases that we have to deal with. It usually begins in the neck, but quickly attacks glands in other parts of the body, most frequently the axilla. If recognized very early it may be possible to prevent the disease from spreading to other glands, but it must be acknowledged that this is seldom if ever done. Operative treatment is almost always unavailing, for the reason that some infected glands are always left behind, and Butlin states: "I cannot discover any instance in which a thoroughly successful removal has been accomplished."

R. C——, aged 19 years. There was no history of malignant disease in the family, and the patient was apparently well until July, 1894, when a swelling was noticed in the left supraclavicular region. This was removed by operation in November, 1894. Two months later, a small swelling was observed in the left axilla. The following July there was a large tumor, the size of an egg, in the left cervical region, freely movable, and in addition there were similar tumors in both axillæ, one the size of an orange, the other that of a hen's egg. The patient was treated for four weeks with the mixed toxins of erysipelas and bacillus prodigiosus. Temporary diminution in the size of the tumors and increased mobility followed. After this time improvement ceased, and the tumors again began to increase in size. In October marked ascites developed. Tapping was performed by Dr. H. Lilienthal of Mt. Sinai Hospital.

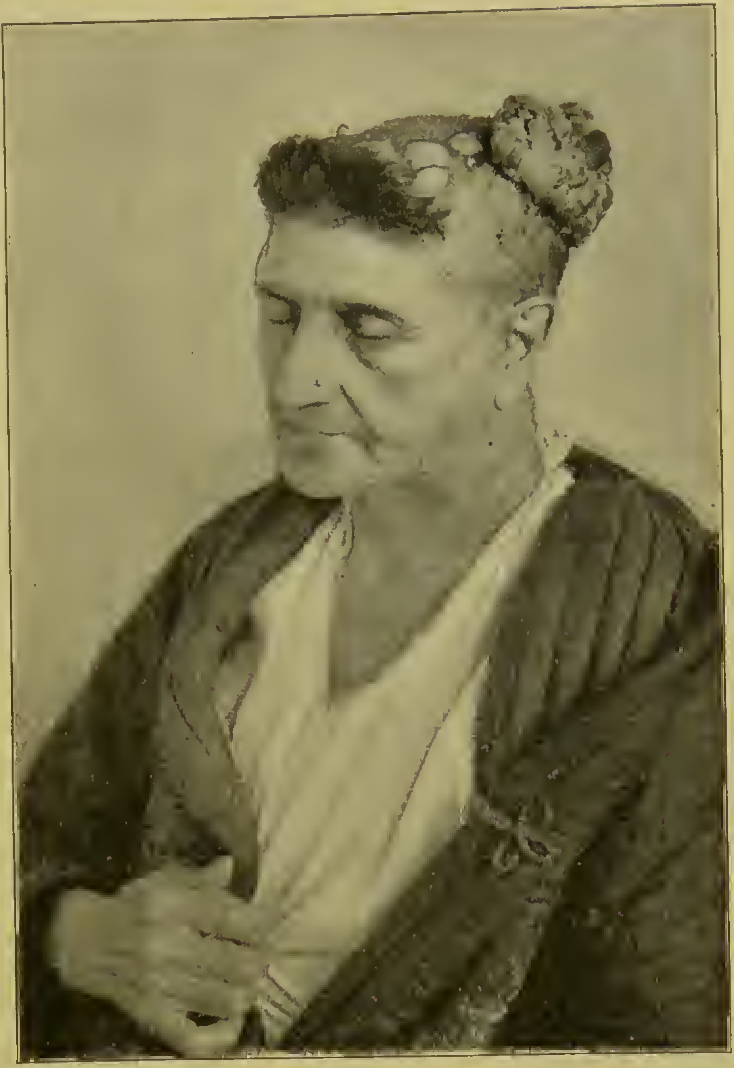

FIG. 27.—Sarcoma of the Scalp.

The ascites proved to be one of the rare cases of chylous ascites. Five quarts of milky fluid were withdrawn every day. The general condition of the patient gradually became worse, and he died in November. Microscopical examination showed the growth to have been a round-celled lymphosarcoma.

In the early stage the *diagnosis* is extremely difficult, and when the disease has become well developed operative procedures are fraught with much risk and offer but the smallest hope of cure. I have observed sixteen cases of primary sarcoma in the lymphatic glands and cannot report a single cure.

TREATMENT BY MIXED TOXINS.

The treatment of inoperable sarcomata by the mixed toxins of erysipelas and bacillus prodigiosus, which was first used by the author in 1892, was the result of gradual evolution from the earlier experiments with the streptococcus of erysipelas and its toxins. The mixed toxins have been employed during the past six years in a large number of cases of inoperable sarcomata and also in a considerable number of inoperable carcinomata. The results in carcinoma, however, were so unsatisfactory that the treatment has been practically abandoned in this class of cases. During the first years this method was very justly looked upon as entirely experimental, and the profession wisely reserved judgment as to its value. The following is a brief account of the method and its results. An earnest effort has been made to eliminate the personal element and to deal with the facts in an entirely impartial and judicial manner. The results of the method in my own cases, as well as those of a considerable number of cases treated by other surgeons, have been reported in detail in *The Journal of the American Medical Association*, August 20th and 27th, 1898.

The preparation of the toxins which has been found by experiment to be the most efficient consists of the mixed, unfiltered toxins of the streptococcus of erysipelas and bacillus prodigiosus, grown together for two weeks and sterilized by heating to 58° C. In children and in patients much reduced in strength, it is better to use the filtered toxins. This preparation is much weaker than the unfiltered, the relative strength being about 1 to 10. However great the difference of opinion may be as to the part the bacillus prodigiosus plays in causing the disappearance of sarcoma, the fact remains that all of my own successes, as well as those of other surgeons, have been obtained with the combined toxins, and I am quite convinced that the process of degeneration of the tumor tissue is greatly increased by the addition of the prodigiosus.

Many opinions have been expressed as to the nature of the process by means of which a cure is effected in the successful cases. The opinion which has been most generally advanced—though resting on theoretical rather than on practical knowledge—is that it is a simple necrosis or sloughing process, resembling that following the injection of any powerful escharotic, like carbolic acid. Consequently, it has been regarded as an entirely local process. This is far from the truth. While in some cases of soft round-celled sarcoma the rapid breaking down of the tumor would lend support to this view, there are many cases that absolutely disprove its correctness. In number of cases the sarcomata have disappeared entirely by absorption, with no breaking down; and furthermore, in several cases the injections were made remote from the tumor. This proves the action to be systemic as well as local. The toxins in some way, acting probably through the blood serum, cause a necrobiosis with fatty degeneration of the tumor cells, the breaking down and formation of the slough depending entirely upon the preponderance of the cellular elements over the intercellular or fibrous stroma. In the spindle-celled variety absorption without breaking down is the more common process, while in the round-celled type the reverse is true. Usually, when possible, it is better to give the injections locally; a much larger quantity can, however, be safely given subcutaneously than when injected into the tumor, and this is a point of much practical importance. A severe chill and rise of temperature to 105.5° F. have been known to follow the injection of one-half minim of the mixed, unfiltered toxins when made into a highly vascular sarcoma. The severity of the reaction depends largely upon the rapidity of absorption.

The rule should be to begin with a minimum dose—for example, one-half minim—and slowly increase daily until the desired reaction has been reached. If this rule be carefully observed, the element of danger is exceedingly small. Inasmuch as the dose depends largely upon the virulence of the cultures from which the toxins are prepared, and since it is extremely difficult to keep cultures of the same degree of virulence, the dose must vary within certain limits, and can be determined in the individual case only by trial, the temperature furnishing the guide. The initial dose should never be larger than one-fourth to one-half minim; boiled water may be added for the proper dilution. The aim should be to give sufficient to produce a temperature of 101°-103° F. In some of the successful cases not more than three or four chills were produced during the entire course of injections, and frequently patients have steadily gained weight while under treatment. This controverts the statement of some writers that the treatment is exceedingly depressing and causes rapid emaciation. This may be true if the doses are too large, but not when the treatment is judiciously carried out. Strychnine may cause speedy death or act as an excellent tonic, according to the amount administered.

The strictest precautions should always be taken to guard against infection, for the reason that a patient is unusually liable to infection from other germs while taking the toxins. The skin should be rendered aseptic and the needle be sterilized by being passed through an alcohol flame before and after using.

Duration of Treatment.—It is possible in most cases to tell within a comparatively short time whether or not the toxins are likely to be efficacious. If no improvement is noted at the end of three weeks, there will be little use in continuing the treatment. In many cases marked improvement is seen within a week after the first injection. If improvement occurs, the treatment should be kept up until the tumor has disappeared or until it is evidently again increasing in size.

Dangers.—The question of the cumulative action of the toxins if the treatment be long continued is an important one. The toxins are rapidly eliminated, and that no harm is likely to result from prolonged treatment is evidenced by the following cases:

In one case the toxins were administered steadily two or three times a week for a period of two and one-quarter years; the patient gained ten pounds in weight and remained in perfect health the entire time. In a second case the treatment has been continued, with few intervals of rest, for a period of nearly four years, with no ill effects. I have personally seen two deaths from the treatment and I have known of six others in the hands of other surgeons.

Results.—Out of a total of 140 cases treated by myself, 84 were round-celled; 21 spindle-celled; 6 mixed; 9 melanotic; 2 chondrosarcoma; 6 sarcoma, in which the clinical diagnosis was not confirmed by microscopical examination; 12 sarcoma, in which the type of cell was not stated, though the diagnosis of sarcoma was confirmed by microscopical examination. Of the 84 round-celled sarcomata, 35

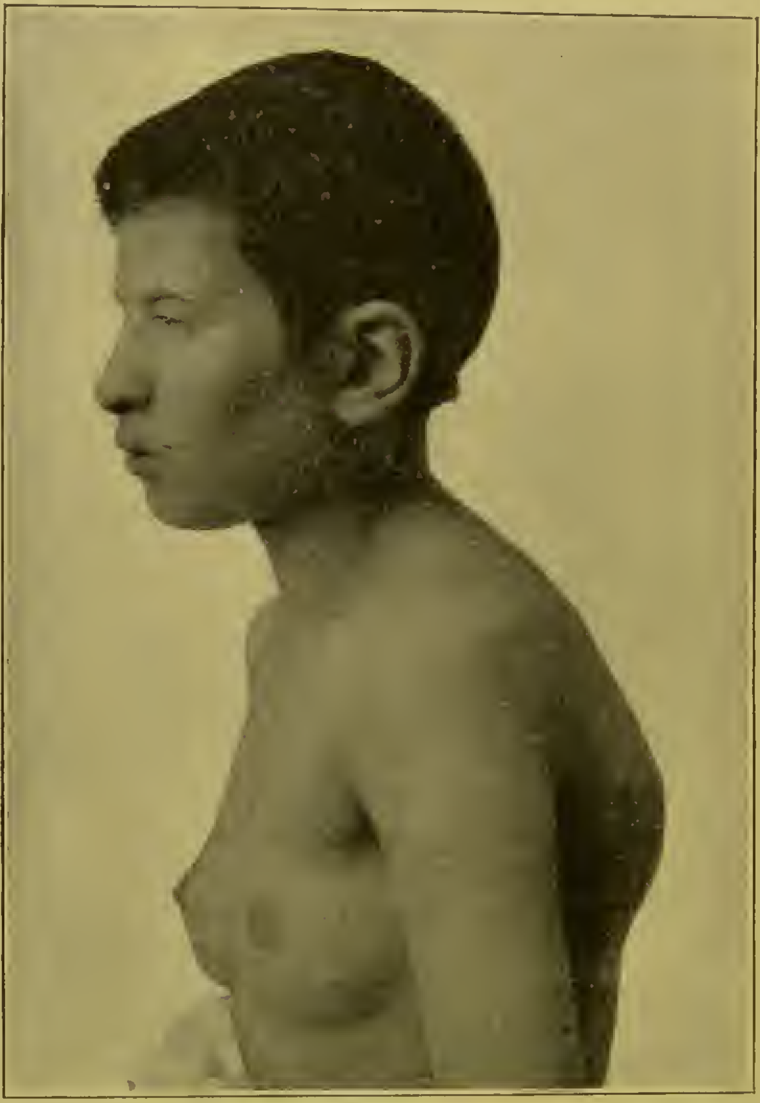

FIG. 28.—Spindle-celled Sarcoma. Scapular region. Entire disappearance under the treatment with the mixed toxins. Patient well, without recurrence, more than four years afterwards.

were more or less improved; 3 disappeared entirely, 1 patient remaining well upwards of three years, 1 now well after one and one-half years, and the third well at the end of one year, when he was lost sight of. Of the 21 spindle-celled, 10 disappeared and all the others showed marked improvement. Of the 6 mixed-celled, 3 improved; 2 were unimproved; 1 disappeared and the patient remained well for three and one-quarter years, at the end of which time there was a recurrence in the abdomen, which proved fatal after six months' time. Of the 10 cases of melanotic sarcoma only 2 showed slight improvement, the remainder being unaffected by the treatment. One large chondrosarcoma disappeared, recurred at the end of seven months, and finally proved fatal; the other was slightly improved. Of the 12 cases in which the type of cell was not known, 6 were improved, 5 unimproved, and 1 tumor disappeared. Of the 6 cases not confirmed by microscopical examination, 2 osteosarcomata disappeared, 2 improved, and 2 remained unimproved.

Summarizing the results obtained, we find: Well over three years, 8 cases; well from one to three years, 9 cases; well from six months to one year, 4 cases; recurred after having once disappeared, 4 cases —2 of these patients died, 2 are still living in good health after further treatment. One of the patients, well one year, has recently had a recurrence.

From published reports and personal communications, I have been able to collect 36 cases of inoperable sarcomata in which the tumor completely or very nearly disappeared as a result of the treatment in the hands of other surgeons. In 26 of these cases the tumor entirely disappeared. Of the total number, 10 were spindle-celled; 11 were round-celled (1 giant-celled); 1 myxosarcoma, and 1 endothelial sarcoma; in 10 cases no microscopical examination was made, though careful examination by a number of surgeons rendered the clinical diagnosis scarcely open to question. In the remaining 3 cases the diagnosis of sarcoma was confirmed by microscopic examination, but the type of cell was not stated. In addition, in 5 of the 10 cases not confirmed by microscopical examination there was a history of recurrence after operation. Of the 36 cases 9 are now well upwards of three years; 9 from one to three years; in 6 cases the disease recurred in other regions of the body at varying intervals of from six months to two years after the disappearance of the primary growth. This latter fact alone—that the disease recurred elsewhere—is sufficient to establish the correctness of the original diagnosis of sarcoma.

The Action of the Toxins upon the Different Types of Sarcoma.—It is evident from a study of the cases reported that the influence of the toxins varies greatly, according to the type of the sarcoma, being most marked in the spindle-celled, and least in the melanotic variety. It is a significant fact, and one of great importance from a pathological standpoint, that in one-half of the cases of inoperable *spindle-celled sarcomata* treated with the toxins the tumors have disappeared entirely, and every case showed a marked improvement. Of the cases of round-celled sarcomata about one-half showed more or less improvement, the other half failing to show any effect from the treatment. In many cases the improvement was but slight and temporary in character; the tumors at first showed decrease in size, a little later they remained stationary, and then after a longer or shorter interval again increased in spite of the treatment. A considerable number of round-celled sarcomata have disappeared entirely and there is reason to hope for a permanent cure.

The melanotic variety, as I have said, is the least influenced of all. I have treated ten cases of melanotic sarcomata, and in no case was there more than a slight, temporary improvement. It is true that most of the cases were multiple and very far advanced at the time the treatment was undertaken; yet in one case the injections were begun immediately after primary operation as a prophylactic measure, but this did not prevent speedy recurrence. Were it not for the fact that there is a case of advanced melanotic sarcoma on record which was cured by accidental erysipelas I should look upon this variety as entirely hopeless. The varying action of the toxins upon these different types of sarcoma lends support to the opinion expressed by Bland Sutton in his book on "Tumors, Innocent and Malignant," which is as follows: "The opinion that all varieties of cancers are due to one cause, assuming cancer to be the product of such agents as produce tubercle, glanders, and actinomycosis, it is much more probable that under the term cancer, many tumors are grouped together on account of structural likeness that have a widely different cause; and the same view holds good for sarcomata and epitheliomata."

Again, writing in 1892, the same writer states: "Sarcoma is probably the scene of action of a violent and prolonged contest between irritant microorganisms and leucocytes. I say probably, because, as has been already remarked, pathologists have not yet succeeded in isolating specific bacteria for sarcomata in general. That such agents will soon be discovered is in the highest degree probable, because in recent years the list of infective granulomata is made at the expense of sarcomata. The structure, mode of growth, infective properties, and manner in which these tumors destroy life clearly coincide with what is positively known in regard to infective granulomata."

I will here repeat the opinion which I have expressed in an earlier paper, in 1892, that I believe this curative action of the streptococcus of erysipelas and its toxins can be explained only on the ground that sarcoma is of microparasitic or infectious origin. Furthermore, I believe this action in itself furnishes very strong evidence in support of this theory. It is a well-known fact that the streptococcus of erysipelas exerts a powerful influence upon tuberculous and syphilitic lesions, both due to a specific microorganism, and so far as we know it has no effect upon any form of tumor not of infectious origin unless we exclude sarcoma and carcinoma. Several links in the chain of evidence have been added during the past two years through the experiments of Juergens, of Berlin, and notably through the more recent researches of Roncali and Sanfelice of Italy. These experiments have been so convincing that so conservative and careful an observer as Dr. Roswell Park in his recent paper on the "Etiology of Cancer," read before the American Surgical Association, states: "Without going so far as to say that this can be done in every instance and that all cancers are necessarily of parasitic origin, one is justified by these results in at least maintaining that some cancers are positively of such origin. If upon this experimental ground one should infer that all cancers are parasitic manifestations, he would do, as will be seen, little violence to the laws of evolution."

I have been more than surprised to find that surgeons for whose ability and judgment I have the highest regard, find it almost impossible to believe in the efficiency of the toxins of erysipelas, although they fully admit the beneficial and curative properties of accidental erysipelas in malignant tumors. The more we study the life history of pathogenic germs the more certain do we become that their influence upon man and animals is chiefly the result of the toxins they produce; therefore, admitting, as we must, the living streptococcus of erysipelas to have a curative action on malignant tumors, theoretically, we have the strongest reason for believing this action to be due to the toxins. The result of practical experience is in strict accord, as we have seen, with theory.

It would be somewhat remarkable that these cases should be the first and, thus far, the only ones with both clinical and microscopic diagnosis of malignancy to disappear spontaneously; and it would be more remarkable still that this disappearance should be coincident with the beginning of the treatment with the toxins. Furthermore, it would be clearly unfair to rule out these cases on the ground of errors in diagnosis without ruling out the cases of cures following operations for sarcoma. Both have been subjected to the same standards of diagnosis, with this important difference: that the cases treated with the toxins have been subjected to *far* *more severe tests*, inasmuch as in most cases the clinical and microscopic diagnoses were confirmed by a number of the best surgeons and pathologists.

I admit that there is difficulty in always being able to differentiate between a tuberculous or syphilitic tumor and sarcoma; but this applies only to round-celled sarcomata, and not at all to the spindle-celled variety, which, as Dr. Welch has pointed out, must be classed as a genuinely malignant tumor. If the successful cases were confined entirely to the round-celled variety of sarcoma, there might be some little weight to the argument; but inasmuch as the majority of the successful cases have been spindle-celled sarcoma, a type of tumor in which error of diagnosis is practically impossible, the tuberculous or syphilitic theory falls to the ground.

Conclusions.—A careful study of my own cases as well as those thus far treated by other surgeons justifies, I believe, the following conclusions, which, I might add, are in almost perfect accord with those recently published by Moullin (*Lancet*, February 5th, 1898):

I. A considerable number of inoperable sarcomata, the correctness of the diagnosis of which is beyond question, have entirely disappeared under this method of treatment.

II. A large proportion of these cases have remained free from recurrence more than three years after treatment—the period which has generally been accepted as of sufficient length to justify their being regarded as permanent cures.

III. Different varieties of sarcoma differ widely as regards the manner in which they are acted upon by the toxins. The results thus far show the treatment to be most successful in the spindle-celled variety, one-half of the spindle-celled sarcomata so far treated having disappeared. Round-celled sarcomata yield less readily, although a certain number have been successfully treated. No case of melanotic sarcoma has, up to the present time, shown more than slight improvement.

IV. The action of the toxins upon sarcoma must be regarded as a rapidly progressing necrobiosis with fatty degeneration. This action is not the result of inflammation, nor does it resemble the destructive action of a local escharotic, but it is rather specific in character, exerting a direct influence upon the tumor cells.

V. The specific action is further confirmed by the fact that several tumors have entirely disappeared when the injections were made subcutaneously, remote from the tumor.

VI. This method of treatment is attended with some risk, unless certain precautions are taken. The chief dangers to be guarded against are: (1) Collapse from too large a dose of the toxins or from injections into a very vascular tumor; (2) pyæmia from insufficient precautions as regards asepsis, especially in cases in which there is a granulating or sloughing surface. (That the risks are small is shown by the fact that in upwards of two hundred cases treated personally death was caused by the injections in but two, one of which was so nearly moribund that no treatment should have been begun.)

VII. The use of small doses of the toxins for a short period after primary operation, as a prophylactic measure, theoretically has much to recommend it, and if proper precautions be observed, the treatment should be practically free from risk.

VIII. The action of the toxins of erysipleas upon sarcomata, as shown by clinical results, is in strict accord with the known action of the living streptococcus of erysipelas; therefore the method has a perfectly logical and scientific basis.

IX. The toxins to be of value must be prepared from highly virulent cultures of the streptococcus of erysipelas.

Dr. B. H. Buxton of the Loomis Laboratory (Cornell Medical School) deserves great credit for his most careful and scientific work during the past six years, in developing and improving upon the methods of preparing the toxins.

MALIGNANT NEW GROWTHS OF THE SKIN.

BY

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BOSTON.

MALIGNANT NEW GROWTHS OF THE SKIN.

CARCINOMA CUTIS.

Under the heading cancer of the skin two varieties of cutaneous lesions are usually described. These belong to the rarer forms of the disease, and occupy the attention of the general surgeon rather more than that of the dermatologist.

1. *Lenticular Carcinoma.*—This is as a rule a secondary affection, and its most common seat is the female breast. It is seen most frequently in or near the cicatrix following an operation for cancer of the breast. It has been said to be the result of an incomplete removal of the disease, and this, in a broad way, must be regarded as true; yet many such recurrent cases are seen after a most radical operation has been performed by a competent person. Occasionally it appears as a secondary infection of the skin above a cancer of the breast that has not been operated on. It appears in the form of white or reddish papules, with a smooth, glistening surface, projecting above the level of the skin in most instances, sometimes, however, not elevated. These papules may increase from small pea-sized lesions to large nodules and tubercles, and by their coalescence form large thickened plaques of indurated skin. Enlarged blood-vessels are often seen over these indurated areas, which are shining and tense as a rule. This is the form of disease that has been described by Velpeau as cancer en cuirasse. In certain instances large areas of the chest are covered with these masses of infiltration. In some cases this cancerous tissue breaks down and a rapidly progressive ulcer is the result, which may lead to excessive marasmus and death. In other cases, ulceration does not occur, but respiration may be interfered with by the mechanical action of the growths or extensive œdema of the arm may result from compression of the lymphatic vessels. In some instances the earlier papules or tubercles may be entirely absorbed, while others of a more malignant clinical nature make their appearance. Occasionally large portions of the trunk may be covered by these cancerous areas. This form is, as has been said, usually secondary to a cancer of the breast, but in a few rare instances it has been

described as an affection primary in the skin. Death may occur, in this form, not only from the cachexia and wasting caused by large ulcerated areas, but also in consequence of metastases in internal organs. Morrow has described a case of very extensive distribution in which large numbers of milia-like bodies were scattered over the affected area.

2. *Tuberose Carcinoma.*—This variety is still more rarely met with than the lenticular form. It is apt to occur at or after middle age, and may be a primary or secondary manifestation. It makes its appearance in the form of papules, nodules, or tubercles, larger as a rule than those of the lenticular variety, very firm in consistence, and deeply seated in the skin and subcutaneous tissues. It may appear upon any portion of the body. The nodules may be discrete and very numerous, or they may coalesce to form hard, irregular masses, which break down and cause extensive and wasting ulcers. They extend in growth upwards to the epidermis, and give to the overlying skin a dark blue or reddish-brown tint. In a remarkable case of Röseler's, often quoted, the whole surface of the body was covered with large and small tumors which broke down about six months after the onset, causing ulceration and death. Frequently, metastases are found in the internal organs.

Anatomically these forms are alike, consisting of epithelial cells enclosed in alveoli surrounded by a wall of connective tissue, and metastasis is produced by the transmission of the epithelial cells through the lymph channels.

The *diagnosis* usually lies between these forms and multiple sarcoma. If the clinical appearances are not sufficient for the diagnosis recourse may be had to the microscope.

The *prognosis* is absolutely unfavorable. Robinson states that two years is a long period of duration, even in the mild cases. In Röseler's case the duration was eight months.

Treatment is of little or no avail. Spontaneous disappearance never occurs and surgical interference can be only palliative.

Pigmented Carcinoma.

It has been the generally accepted view that almost all of the malignant growths arising from nævi are sarcomata. Unna, by his investigations of nævi and nævocarcinomata, has thrown doubt upon this belief. His investigation of so-called soft moles in infants or children showed them to be made up of cellular cords which have a direct connection with the surface epithelium or the prickle layer of the hair follicles and sweat glands. The cellular "cords" consist of small cubical or elongated cells, which have a large oval nucleus and are very similar to surface epithelium, except in the fact that they have no fibrillæ. These cords have a tendency to snare themselves off from the fibrillated epithelium and are then surrounded by connective tissue and isolated. Hence he regards the soft nævi as epitheliomata; and from this fact, and from the results of his investigation of some cases of supposed melanotic sarcoma developing from nævi, which he found to be alveolar carcinoma, he throws much doubt on the previously accepted view that almost all malignant outgrowths and metastases from nævi are sarcomata.

These tumors, arising from moles, appear as hard or soft and elastic nodules, of a dark, bluish-black or slate color, and either rapidly increase in size and ulcerate or may in some instances remain stationary at a given period of their growth. They may assume a warty or fungous character, and secondary nodules may appear in their vicinity. As a rule metastatic nodules soon occur in the internal organs, and there is rapid marasmus, followed by death in a short time. Metastatic nodules may occur along the course of the lymphatics. Clinically it is difficult, if not impossible, to differentiate this form of carcinoma from sarcoma, and the investigations of Unna have, as has been said, thrown much doubt upon the true sarcomatous character of many cases of malignant disease arising from moles that have hitherto received this histological interpretation.

Epithelioma.

There is not as yet complete unanimity in the use of the terms carcinoma and epithelioma as applied to neoplasms of the skin. The weight of authority, however, is now in favor of regarding all carcinomata as of epithelial origin; so that any epithelial new growth of the skin of malignant character may be called carcinoma. There has been a tendency of late to include both the malignant and benign epithelial neoplasms of the skin under the common name of epithelioma; but the term epithelioma, as applied to the skin, is still generally understood to refer only to the malignant new growths of epithelium, and it is in this sense that it is used in this article.

VARIETIES.

Three forms of epithelioma occur upon the skin: the superficial, discoid, or flat; the deep-seated or nodular variety; and the papillary. As Robinson remarks, this distinction is not an absolutely true one, as a deep-seated epithelioma may have originated from a superficial one, a primarily deep-seated one may have become superficial, or either may have changed into the papillary variety.

Superficial, Discoid Epithelioma.

This variety usually makes its appearance in the form of small, pinhead-sized papules, smooth, glistening, pale red or pearly in color, and very firm to the touch. They are either scattered about singly or arranged in groups, and at times may take on a linear form. They may remain for a long time very small, or they may enlarge to the size of a pea. A fissure or excoriation often occurs at their summit, the result of scratching, and they are then covered with small crusts. In many instances they may retain their benign character for many years, showing no tendency to break down and ulcerate or to increase in numbers. After a longer or shorter time, however, a change usually takes place, and new papules begin to make their appearance at the periphery. These papules are very characteristic, being of a white, shining, "mother-of-pearl" appearance, firm to the touch, but easily expressed from the skin. They break readily between the fingers and are found to be composed of epithelial cells arranged in groups. Various names have been applied to these bodies, such as epidermic globes, cancroid corpuscles, pearly bodies, etc.

Sooner or later ulceration begins in the central or oldest lesions. This ulceration varies in appearance, sometimes remaining superficial for a long period, at other times progressing rapidly in depth. It is a rounded or polygonal loss of tissue, with a reddish floor, and produces a viscid secretion, which forms a glistening coating when dry. The edges are sharply bounded and firm to the touch, and scattered here and there are usually found the hard, pearly bodies described above as characteristic of cutaneous epithelioma. The growth may be completely exfoliated in the centre, and healing produced with the formation of a cicatrix. This healing at the centre and continuous progression at the periphery often give rise to circinate and serpiginous forms, and large portions of the skin may be thus affected. Very exceptionally the formation of epithelial pearls at the periphery may cease and the affection, after existing for a long period, may heal spontaneously with the formation of a cicatrix. Sometimes the active, progressive edge is very narrow and we get the appearance of a small ulcerated groove completely encircling a cicatricial area. The superficial form may in its progression extend more deeply, when we find the centre of the ulcer much depressed below the surface and the edges elevated and sharply contoured. Where secretion is abundant, the centre may be covered by dark crusts, which on removal expose the characteristic floor of the ulcer, made up of epitheliomatous tissue which yields readily to the curette. Papillary outgrowths may appear at the edges. This flat form of epithelioma does not as a rule produce any ill effect upon the general health, nor does it cause enlargement of the neighboring lymphatic glands, although it may at times extend quite deeply into the subcutaneous tissues. This form may appear upon any portion of the body, but is seen most frequently on the upper part of the face, and may arise from apparently normal skin, or have its origin in a senile wart, or in ulcerations from other pathological processes, such as tuberculosis, syphilis, etc.

Deep-Seated or Nodular Epithelioma.

The superficial or discoid form may, as has been said, be converted into this variety, or the latter may be a primary manifestation. The deep-seated form appears as firm, closely aggregated nodules, or as a single nodule, which may attain the size of a pea. These nodules occupy the entire thickness of the skin and extend into the subcutaneous tissues. They gradually grow into a smooth, hard tumor, with a shining reddish surface, traversed often by dilated vessels, and made up of irregular nodules. The centre is often retracted, giving an umbilicated appearance. As the disease progresses, it may extend into the surrounding tissues, and form a hard, diffuse mass, recognized only by the touch.

After a time the tumor breaks down and an ulcer is formed. This ulcer is deep, irregular, with hard everted edges which contain the epithelial pearls. It may go on to the involvement of muscles and bones in the cancerous process, and cause deep destruction. Sometimes the parts may be thrown off by necrosis and an attempt at repair be begun, but the process in the mean while spreads in other directions. The lymph glands later become involved, and death occurs from marasmus and from metastases in the internal organs. This form is of common occurrence upon the mucous membranes.

Papillary Epithelioma.

Apart from the papillary character that many of the epitheliomata assume in common with tuberculosis, syphilis, etc., a primary papillary epithelioma sometimes occurs which is apt to pursue a very malignant and rapid course. It may begin as a superficial, indurated elevation, or it may be provided with a pedicle and project sharply above the surface. It is seen often upon the mucous membranes or at the junction of the mucous membranes and the skin, and also upon the scrotum. It is reddish or shining at first, but later becomes fissured and is converted into an ulcer, at first flat and superficial, afterwards deep-seated and extensive. The lymphatic glands may become affected, and death results as in the deep-seated variety. The papillomatous character of the growth is evident before ulceration occurs, and fungous, cauliflower appearances are often produced. These growths are very vascular, of a bright red color, and bleed easily. Crocker states that their average duration is four years.

Certain forms of cancer of the skin have been described as occurring in persons who were engaged in special occupations. Thus Percival Pott called attention to *chimney-sweep's cancer of the scrotum*, which has been observed in England and is supposed to be caused by the irritation of soot. Butlin has asserted that this affection is very rare on the Continent on account of the greater cleanliness and the increased precautions that are taken. There is a preceding condition of chronic eczema and a wart-like state of the skin of the scrotum. Ulceration finally occurs, and may be very extensive unless operative interference is called in. There is often an involvement of the inguinal glands. Tar and paraffin cancer has been described by Volkmann, which affects those who work in coal tar and paraffin. It occurs most commonly on the scrotum and arms.

Rodent Ulcer.

This form has also been called Jacob's ulcer, ulcus exedens, *noli me tangere*, etc. First described by Jacob of Dublin in 1827, it has since figured as a separate affection in all of the English text-books. Modern opinion is distinctly in favor of viewing it simply as a clinical variety of epithelioma. The English, who are chiefly responsible for its prominence, describe the lesion as beginning as a soft, flattened nodule with smooth surface and quite vascular. It is not very uncommon in elderly people and appears on the eyelid, nose, or upper two-thirds of the face, and may remain without enlargement or ulceration for many years. As years go on, however, there is a tendency to break down, and when ulceration finally sets in it is progressive, although it may be very slow. It continues its obstinate course, eating in both laterally and downwards, and eventually attacking the bones, and it may result in the destruction of the greater part of the face before death occurs from exhaustion. The points that have been advanced as differentiating this ulcer from the superficial epitheliomata are in the first place the fact that the amount of new growth is very slight compared with the extent of the ulcerated surface. The edge is characteristic, being only slightly raised or rounded and not everted. There are none of the warty outgrowths seen at the borders of an epithelioma, and the neighboring lymphatic glands are never affected, so that it remains a local affection throughout its entire course.

These ulcers are but slightly painful. Sometimes a typical deep-seated epithelioma may develop from a rodent ulcer, which is an argument against those who claim for the latter affection a distinct and separate place.

"Crateriform ulcer" has been described by Hutchinson as occurring in about the same position and at about the same age as rodent ulcer, and Crocker declares that nearly all of the cases that he has seen have developed from a previous rodent ulcer. It is a much more rapidly progressive affection than the latter, however. It is a hard nodular tumor with a distinct depression in the centre, where there has been ulceration, and the surrounding margins are very high and firm. It is much more resistant to the curette than rodent ulcer, and histologically the type varies from that of the latter.

Rodent ulcer is most common between the ages of fifty and sixty. Cases have been reported in England, however, as beginning as early as fourteen and sixteen years. In the former case the patient died of the disease at thirty-six years of age.

On the whole there is not sufficient evidence to warrant the separation of this form from the epitheliomata. Other varieties of epithelioma may at some period of their course take on the appearances of rodent ulcer, and, as will be shown in the section on pathological anatomy, there are no histological appearances that are incompatible with the view that it is a simple clinical variety.

LOCALIZATION.

The face is the most frequent seat of epithelioma, and especially its upper half, including the eyelids, the cartilaginous and bony parts of the nose, the forehead, lips, and cheeks. Next in order of frequency come the genitals, the extremities, and the trunk, including the neck. Eighty-five per cent. of all cases are said to occur on the face and scalp. Very often the same places, and especially the eyelids, temples, and nose, may remain affected by the disease for a long period without marked increase. Upon the forehead the ulcer may be of the serpiginous form, and may retain the same character for many years, or it may extend deeply and involve the bones. When situated upon the nose, the nasal bones and superior maxilla are often attacked.

Epithelioma of the Lip.—In this situation it is vastly more common on the lower lip than on the upper, and epithelioma of the lower lip is almost wholly confined to men, women being very rarely affected. When on the upper lip, a rare situation, it is found to affect women rather more frequently than men. Instances of apparent autoinoculation from the lower lip to the upper have been recorded. When upon the lower lip the affection is usually at one side of the median line, and at about the junction of skin and mucous membrane. It begins either as an excoriation or abrasion, or as a small papule which gradually increases in size and becomes indurated. Sometimes the tumor may attain considerable size before ulceration begins; at other times it breaks down quite early in its course. The ulcer is usually covered with a crust and has elevated margins, deeply infiltrated and very hard in consistence. It may progress rapidly and lead to destruction of the hard palate and the bones of the face, with involvement of the lymphatic glands, extensive ulceration, marasmus, and death.

Epithelioma of the *tongue* or *mucous membrane of the mouth* is a not infrequent occurrence. It develops from the thickened, warty, white patches, known as leucoplakia, sufficiently often to warrant the belief that there is some causal relation between the two processes. Leucoplakia may arise as a sequel to syphilitic lesions of the tongue, or it may be caused by the irritation from smoking. Epithelioma of the tongue begins either as a small, red, raw surface, painful on pressure; as a nodule; or as an excoriation or fissure with soft edges. Soon the edges of the ulcer or the nodular formation become hard and infiltrated, and the disease makes rapid progress, infiltrating the submaxillary glands, and often causing metastases in the internal organs. The extension of the growth is often accompanied by much pain, of a lancinating character. Epithelioma of the mucous membrane of the cheek is not so common, and when present is usually flat, with raised edges.

In epithelioma of the *genitals*, the glans penis or the scrotum is usually the first to be affected. Reference has already been made to "chimney-sweep's cancer," and to that occurring in tar and paraffin workers, in whom the affection is situated on the scrotum. The labia majora are the parts usually attacked in women.

Epithelioma of the *extremities* is very apt to develop from ulcers, scars, and places that are exposed to external violence, especially the backs of the hands and upper arms. It sometimes arises from the stumps of amputations.

The *trunk* is the least common of all situations for epithelioma, and here the umbilicus, the nipples, and the sacral region are the parts more commonly affected. The anal region is a locality occasionally affected.

PATHOLOGY.

As the pathology and etiology of epithelial cancer in general are exhaustively treated in another part of this volume, we need discuss only some of the features that are peculiar to the various forms here described. The epitheliomata that affect the skin are all derived from pavement epithelium, and they are usually divided into two forms—the lobulated and the tubular. In the lobulated form the different varieties of cells are seen that we meet with in a section of normal epidermis, including the rete Malpighii and the overlying layers. The picture is that of successive layers of epithelial cells, with a concentric arrangement, so that at the centre we find the more or less cornified cells of the horny layer. These central cells have in some instances undergone a colloid or fatty degeneration. The origin of these epithelial outgrowths is the rete Malpighii. Epidermic "globes" are seen in these outgrowths, especially in the deep-seated epithelioma.

The tubular epithelioma shows little tendency to the formation of epidermic "globes" containing horny tissue. It originates usually from the rete Malpighii or from the hair follicle. The cells of which this form of epithelioma is made up are smaller than those of the lobulated variety and correspond to the lower rete cells. It has been the subject of much difference of opinion how much part the glandular structures of the skin take in the origin and production of epithelioma. Darier has shown by his studies that the sebaceous glands are rarely the starting-point of these growths, notwithstanding the fact that the arrangement of the epithelial cells in some instances suggests the form of these glands. In cases in which the shape and arrangement of the sweat glands were simulated by the cell masses it has been assumed that they were derived from these glands. Fordyce has examined many such cases, and could frequently trace their origin to the interpapillary rete processes, the sweat glands being unaltered, and he considers that while it is possible that both sebaceous and sweat glands may give rise to epithelioma, it is impossible to prove this on account of the early ulceration which destroys the tissues first affected.

With regard to the form that has been described as rodent ulcer, the general view is that it is an epithelial new growth, although opinions still differ as to its origin. Thin and Walker regard it as derived from the sweat glands, Butlin and Thiersch from the sebaceous glands, while Paul and Darier consider that it may have its origin in any of the epithelial structures. Warren believed that it originated from the rete Malpighii; others have looked upon the hair follicles as its starting-point.

DIAGNOSIS.

In the case of any long-standing, obstinate, ulcerated lesion, with hard and elevated margins, in people over forty years of age, the suspicion of epithelioma should at once arise. The hard consistence of the margin is perhaps the most valuable diagnostic mark, but to judge the degree of hardness necessary to warrant the probable diagnosis of epithelioma must be admitted to be a matter of experience. The differential diagnosis will usually lie between syphilis, tuberculosis, and the affection under consideration. Tuberculosis, if in the clinical form of lupus, is rather apt to develop early in life; is very chronic in its course, and is characterized by the typical reddish-brown lupus nodules, which are much softer to the feel than the tissue of either epithelioma or syphilis. The verrucous form of tuberculosis, which occurs chiefly on the hands, could hardly be confused with epithelioma, but some question might arise in the presence of the miliary tuberculous ulcer that is seen at the junction of skin and mucous membrane, a favorite seat also for epithelioma. The points of distinction are the soft character of the tuberculous ulcer, the presence of miliary tubercles at its edges, its association with internal tuberculosis, and the absence of other characteristics of epithelioma. The same may be said of a tuberculous ulcer of the tongue and mucous membranes.

As regards syphilis, it may be a question whether a nodule of the lip or tongue is epithelioma or the primary lesion of syphilis. In the latter, there is a much earlier enlargement of the lymphatic glands below the jaw, and it has not, as a rule, the very hard everted edges of an epithelioma. Sometimes it may be necessary to have recourse to the microscope or to wait for the appearances of secondary lesions. A late syphilitic ulceration of the skin is differentiated from epithelioma by its more rapid course, by the absence of a firm cartilaginous edge, and by its tendency to appear in several foci. Epithelioma may develop on tuberculous and syphilitic ulcers, but will usually present its peculiar characteristics so that recognition is not difficult. Epithelioma of the tongue, and a gumma in this position, are not always easy to differentiate. The epithelioma is very apt to develop upon a patch of leucoplakia, and is as a rule single, while a gumma may be accompanied by other lesions. The epitheliomatous ulcer is apt to have a much harder base with deeper infiltration, and the borders are likely to be elevated and everted, while there may be a papillary outgrowth from its floor. The adjacent lymphatic glands are less likely to be involved in a gummatous than in an epitheliomatous lesion.

PROGNOSIS.

The prognosis varies according to several factors. If the growth is a superficial one upon the skin, radical removal usually gives favorable results, not always permanent, however, as recurrences may take place in the cicatrix. Still, large numbers of these growths are removed without recurrence. If the growth is situated on the borders of the mucous membrane, or on the mucous membrane itself, the prognosis is less favorable, as it is more likely to pursue a rapid course in this locality and to lead to metastases. The deep-seated variety is less hopeful than the superficial, and the rodent ulcer type may be classed with the latter form as regards prognosis. Any of these forms, if allowed to progress untreated, may eventuate in a deep-seated process that it is hopeless to try to cure. Robinson thinks that on the whole the prognosis of epithelioma of the skin under proper treatment is more hopeful than has been assumed.

TREATMENT.

We know to-day of no internal remedies that are of value. Thorough and radical destruction of the diseased tissue is our only hope, and this may be effected by the knife, actual or galvanocautery, curetting, or chemical caustics. Epitheliomata of the tongue and lip are as a rule best treated by excision, and this should be as thorough as possible, a generous margin of the apparently sound tissues being removed. Superficial forms upon the skin may be removed by curetting and applying afterwards a chemical caustic, but curetting alone is insufficient. The small, pearly variety is often effectually removed in this way. A great variety of caustics have been used in the treatment of epithelioma, as in that of tuberculosis, among which may be mentioned acid nitrate of mercury, nitric, hydrochloric, and sulphuric acids, chloride of zinc, arsenious acid, and caustic potash. Many small beginning ulcerated lesions may be well treated by thorough application of strong nitric acid applied with a pointed stick, the lesion being thoroughly bored into in all directions. Nitrate of silver is not to be recommended as its effect is not sufficiently far-reaching, and it may serve only to excite the epithelial tissues to greater activity. Chloride of zinc either as a paste or in stick form is much used and praised by some. My own experience is that caustics are applicable and effective in the small and recent lesions, and should then be used thoroughly and applied well into the sound tissues. In rapidly growing or extensive lesions, and especially when the lip or tongue is affected, thorough excision with the knife is the best treatment. Robinson, who is a warm advocate of the use of caustics as causing less deformity than treatment by the knife, considers arsenious acid the most valuable agent for treating epithelioma. He uses it by mixing it with powdered gum acacia and water so as to form a paste the consistence of firm butter. The strength and the length of time the application is allowed to remain on are to be regulated according to the case, and this is a matter of judgment and experience. The action of the paste must be watched, and the strength of subsequent applications regulated according to the demands of the particular case.

Paget's Disease of the Nipple.

This affection, which has been called "malignant papillary dermatitis" by Thin, was first described in 1874 by Sir James Paget, who, in an article in the St. Bartholomew's Hospital Reports, published an account of fifteen cases in which a chronic inflammation of the skin of the nipple and areola was followed by cancer of the breast. The patients were all women between forty and sixty years of age, and the affection began by the skin of the areola and nipple changing into an intensely red, very finely granular surface, resembling somewhat an acute, diffuse eczema. It was always covered by an abundant, clear, yellowish exudation, accompanied by itching and burning, but without impairment of the general health. Some of the cases looked like an ordinary chronic eczema, others by their dryness and desquamation were more suggestive of psoriasis. Paget admits that precisely similar conditions occur in which the eruption disappears after lasting several months, without being followed by any other affection; but in the cases he records, mammary cancer appeared within one or two years of the beginning of the affection. The cancer never preceded the cutaneous affection. The eruption was rebellious to all treatment, and persisted after the appearance of the cancer. The cancer developed in the gland, not far from the affected skin, but was always separated from the latter by a space of apparently sound tissue.

SYMPTOMS.

Since this description of Paget's, numerous cases have been recorded, and the subject has been amplified by Thin, Butlin, Crocker, Wickham, and others. In most instances the disease occurs upon the breasts of women between forty and sixty years of age. It begins, as Paget has pointed out, as an inflammation of the skin of the nipple and areola, resembling an eczema, and usually appears upon one side only. The edges of the plaque offer several well-defined characteristics. The contour is circinate, composed of more or less regular arcs of a circle. The edge is sometimes raised, and is sharply bounded from the normal skin. The plaques occupy the middle of the breast, the nipple being situated pretty exactly in their centre. The surface of the plaque is bright red, oozing in places or covered with crusts and scales. When a further degree of ulceration has been reached, irregular, confluent islets of epidermis are seen scattered over the excoriated surface; these are dry and glazed in appearance and have been regarded as characteristic of the disease. There is usually much pain caused by contact with the air or with the clothing and dressings, and there are paroxysmal attacks of itching, and in some instances of intercostal neuralgia. At quite an early stage of the affection considerable induration is to be felt, accompanied by retraction of the nipple, which in some instances is very marked. The chief characteristic of the disease lies in the formation of a cancerous new growth. This occurs within a variable period of time after the appearance of the affection, on an average from two to seven years, although it may assert itself much earlier. The cancerous new growth may first appear superficially upon the surface of the plaque, or it may arise in the deeper parts. The lymphatic glands are not affected until a late period of the disease. The breast is gradually invaded by the cancerous growth, and unless operated upon, follows the course of ordinary cancer in this locality.

It cannot be said that Paget's disease is confined absolutely to the female breast. Forrest has reported a case in which it existed on the male breast and Crocker one in which the scrotum was the part affected. The latter was in a man of forty-seven, in whom nodules developed in the centre of an ulcer that had existed for two years. Pick has reported a similar case.

Paget's disease is unilateral, and has a predilection for the right breast. The larger number of cases occur between the ages of fifty and sixty; but it is not improbable that in a part of these there has been some affection earlier than the patient has noticed, as the subjective symptoms are very slight at the outset. Of twenty-three cases collected by Wickham, a cancerous heredity could be determined in but two. No constitutional symptoms accompany this disease.

PATHOLOGICAL ANATOMY.

Butlin, Thin, Crocker, Duhring and Wile, and Darier and Wickham have all written upon the pathological anatomy of the disease. The microscope shows that the pathological appearances cease abruptly at the edge of the elevated border of the plaque. Here the rete is everywhere thickened and undergoing proliferation, as shown by the division of the nuclei that is progressing, and there are numerous polynuclear leucocytes between the epithelial cells. The papillæ are elongated and infiltrated with round cells and there are signs of inflammation throughout the corium generally. In the more central portions the epidermis has disappeared to a greater or less degree, but in some places the interpapillary prolongations are retained and project deeply into the corium. The lactiferous ducts are filled with epithelial cells, and Thin believes that these are the starting-points of the whole disease, and that the process is a cancerous one from the beginning.

Much interest has been added to the study of the pathology by the discovery by Darier of certain peculiar cell forms in this disease, which he regarded as parasites of the order Coccidia, or psorosperms. These bodies are present in large numbers in the epidermis and in the epithelial lining of the lactiferous ducts and of the glands. They are larger than the surrounding epithelial cells, are provided usually with a glistening double-contoured membrane, contain oftentimes several nuclei, and exhibit a protoplasm that does not have the fibrillary structure of the rete cells. These bodies he considers to be the cause of the disease. He regards them as having an intracellular position, which he considers to be proved by the presence, next to the cell wall, of a granular mass, which he takes to be the nucleus of the epithelial cell pushed to one side by the psorosperm that has invaded it. These bodies are found in all cases so far as is known, not only in those occurring on the breast but in the few cases that have been reported in other situations. Darier's theory is that these bodies, which he regards as parasites, penetrate the epidermis through an abrasion of the nipple and start a proliferation of the epithelial elements. He considered his theory borne out by the fact that in other affections in which epithelial proliferation occurs these cell forms are also found, as in keratosis follicularis (psorospermose folliculaire végétante) and in certain epitheliomata. It is now pretty well accepted that the cell forms resembling psorosperms in keratosis follicularis are in reality cells that have undergone an irregular and excessive keratinization, and as no one has been able to cultivate or inoculate the "psorosperms" of Paget's disease, the theory that these are really parasites and the cause of the disease is very far from proved.

DIAGNOSIS.

The following points of differentiation from chronic eczema, the only affection with which it is likely to be confounded, have been tabulated by Wickham: Paget's disease does not, as a rule, begin until between the fortieth and sixtieth year, and usually when the patient appears for advice the affection has lasted a long time, from seven to twelve years on an average. When seated upon the breast the lesions are usually unilateral. It begins with crusts and horny secretions, which are adherent and rebellious, seated at the tip of the nipple, accompanied or not by itching and ulceration of the lower parts, and soon followed by retraction of the nipple. The superficial lesions progress slowly, without spontaneous healing. The border is slightly raised and very sharply bounded. The surface is bright red, in places oozing, slightly granular, and covered in parts with scales and crusts, in which are seen ulcerated points and islets of partially formed epidermis. There are superficial induration and considerable pain and pruritus. There are no vesicles, the lymphatic glands are not enlarged, and treatment for eczema is without avail. Cancer appears either at the surface or in the deeper tissues in from seven to ten years on the average.

Although the cell bodies referred to above cannot be considered, with our present evidence, as the cause of the disease, yet they are characteristic and not found in eczema, so that their presence in the tissue or in the scales would confirm the diagnosis.

PROGNOSIS AND TREATMENT.

If seen in its early stages the prognosis is pretty good. As soon as the diagnosis is made with certainty thorough destruction of the whole affected area should be advised. Excision is to be preferred where practicable; otherwise thorough curetting, followed by cauterization, should be performed. In this way a cure may often be effected. Darier recommends chloride of zinc, 1 : 3, in solution applied for several hours, the wound being dressed with iodoform gauze. Later mercurial plaster is to be applied. Crocker also recommends chloride of zinc, in the form of a paste, as follows:

℞ Chloride of zinc,	℥ xvi.
Powdered opium,	℥ iss
Hydrochloric acid,	ʒ vi.
Boiling water,	q.s. ad ℥ xx.

M. To one ounce of this solution add two drachms of wheaten flour.

This should be spread on lint the size of the affected area, kept on from four to six hours, and the slough poulticed off.

SARCOMA CUTIS.

Sarcoma of the skin may present itself in quite a variety of clinical forms, which are not always well defined from one another. It may occur primarily in the skin as a single tumor; a single tumor after existing for a long time may be followed by a general outbreak; a generalized outbreak may occur without a preceding solitary tumor; and finally, sarcoma of internal organs may be followed by metastases in the skin.

A primary, unpigmented, single sarcoma may develop at the site of an injury or a cicatrix, a nævus, or in or beneath the normal skin. Kaposi has seen it occur at the site of a healed furuncle on the anterior surface of the thigh, and also between the shoulders. The tumors may remain stationary over a long period of years, finally enlarging and giving rise to metastases disseminated over the skin or in the internal organs. On the other hand, a primary local sarcoma may be followed very quickly by general sarcomatosis. The form of the primary tumor is very variable, as is also the size that it may attain before ulceration takes place. It differs from carcinoma in its softer consistence and in its greater tendency to assume a peculiar configuration, such as toadstool and pedunculated forms. It has been claimed that this variety occurs more often in women than in men, and that it is of congenital origin in some instances, although the latter statement must be accepted with caution. This form of sarcoma—and we are speaking now of the primary, local, non-pigmented form—may be eradicated without further dissemination if surgical aid is called in early. The extirpation should be a radical one, as less active measures have sometimes served to increase the growth. Such growths have disappeared after an attack of erysipelas.

A generalized cutaneous sarcomatosis may occur consecutively to a single localized cutaneous sarcoma, or it may have as its origin a sarcoma of internal organs. When metastatic nodules have once made their appearance the progress is apt to be pretty rapid. Shattuck has reported a case of a man who was dead with generalized sarcoma thirty-four days after he first summoned a physician and less than a month from the appearance of the first external lesion. Cases are from time to time seen in which the whole integument is filled with closely aggregated nodules of sarcoma, and at the autopsy all of the important organs are completely studded with small and large tumors. Many of these nodules are not, strictly speaking, in the skin, but arise primarily in the subcutaneous tissue, and then extend upwards.

Apart from these varieties that we have been considering, there are three forms of sarcoma affecting the skin that occupy more exclusively the attention of the dermatologist. These are melanotic sarcoma, multiple idiopathic pigmented sarcoma, and a third form, which is not always well defined and which seems often to be allied to mycosis fungoides and to leukæmia and pseudoleukæmia, called generalized sarcoma or sarcomatosis cutis.

Melanotic Sarcoma.

This form of sarcoma may be primary upon the skin, or it may be secondary to a tumor of the internal organs. As has been said in the section on epithelioma, the investigations of Unna point to the probability that a certain number at least of the cases described as pigmented sarcoma developing from nævi should be classed among the epitheliomata. Until the subject has been more widely investigated, it is best to consider that the majority of malignant growths arising from nævi are sarcomata. The nævi from which these growths spring are usually pigmented and warty in character, and are often seated on the lower extremities. This form of sarcoma may also start from other pigmentary lesions, as chloasma and the staining left from a spot of purpura.

When a pigmented nævus begins to take on a sarcomatous character, there is often seen nothing but a shallow ulceration at first. This may remain so until metastasis has occurred, or soft, bluish-black nodules may make their appearance, which enlarge rapidly and ulcerate. Sometimes these nodules by their coalescence form fungous tumors of a considerable size. As a rule, it is not many weeks or months after the appearance of these primary nodules before secondary manifestations are noted, at first in the vicinity of the primary growth, in the form of similar bluish-black nodular infiltrations, which may unite and occupy large areas of skin. The affection is rapidly transmitted to the internal organs, and causes death within a short time. Occasionally the local lesions may remain stationary for a considerable period before the disease becomes general. The growth is made up histologically of spindle and round cells, with a large amount of pigment both within the cells and in the intercellular spaces. Giant-celled forms are occasionally seen, and the tumors may have an alveolar type.

This form of cutaneous sarcoma is of a very malignant nature and usually proves fatal a few months after its first appearance on the skin. may exceptionally be removed without recurrence, if operative interference is resorted to at a very early stage. Arsenic, internally, is of no avail.

Multiple Idiopathic Pigmented Sarcoma.

Kaposi was the first to describe this form of sarcoma, in 1879. All the cases observed by him up to the publication of the last edition of his text-book occurred in men. From his sixteen cases, and those published by other observers, he notes that it always begins upon the hands and feet and advances upwards over the arms and legs by the appearance of new foci, until in from two to three years it is found upon the trunk and face. It appears as firm, reddish-brown, or purple nodules, from the size of a pea to that of a bean, which are often confluent so that diffuse infiltrations of a purplish color are seen. The hands and feet are usually much swollen and very painful, so that walking is rendered difficult and the use of the hands is much impeded. Sometimes there is seen a diffuse sarcomatous infiltration with very few isolated nodules. Both the extensor and flexor surfaces of the hands and feet may be affected. A peculiarity of this form, which recalls the tumors of mycosis fungoides, is that many of these nodular infiltrations after a time become depressed in the centre and disappear partially or wholly, leaving pigmented cicatrices. The growths upon the extremities rarely ulcerate to any extent, but later, when the disease has invaded the upper portions of the body, deep losses of tissue may occur upon the face and trunk. It is seldom that the lymphatic glands are affected. The mucous membranes are often involved late in the course of the disease, and fever, hemorrhages, and marasmus precede the fatal termination. After death large numbers of similar nodules are found in the internal organs, especially in the descending colon. Instances, however, of complete involution of the tumors, when they have not progressed beyond their primary location on the hands and feet, have been recorded by Hardaway, Köbner, and others.

Histologically the tumors are found to be made up of a purely sarcomatous tissue. Kaposi, who has met with the largest number of cases of this affection, states that the growths are usually of the small-celled variety, although in places the spindle-celled form is met with. Fordyce found in a case examined by him that the neoplasm extended from a point just below the epidermis to the subcutaneous tissue. The tumor was made up of fusiform cells, which extended in bundles in various directions. The growths are very vascular and capillary hemorrhages are frequent; in fact, the growths have been by some termed angiosarcomata. There is much blood pigment in the walls of the vessels and also scattered through the neoplasm generally, and it is from this source that the color of the nodules is probably derived, and not from pigment manufactured by the cells themselves. Tandler has reported an interesting case which he thinks should be put in this category, in which whitish nodules appeared upon the fingers and the elbows, with great thickening about the joints. Histologically, the growth was a spindle-celled sarcoma. The tumors disappeared almost entirely under Fowler's solution injected into the muscles and afterwards taken internally.

DIAGNOSIS.

When the nodular infiltrations are not very far advanced, and are confined to the hands and feet they might be mistaken for a papular syphilide. The diffuse infiltration, if present, would render syphilis particularly improbable. There is also a peculiar violet or purplish tint to these infiltrations that is quite characteristic. Leprosy and mycosis fungoides might be thought of. In leprosy, one would almost surely find other characteristic symptoms, such as anæsthesia and the various deformities that occur in this disease. A bit of tissue examined for bacilli would at once settle the question. It might be more difficult to exclude mycosis fungoides, as spontaneous disappearance of some of the lesions, which is the rule in mycosis fungoides, may occur in the form we are considering. The localization, the absence of a so-called premycosic stage, where urticarial and eczematous eruptions are present, and the histological characteristics, which are those of a true sarcoma, should be sufficient to rule out mycosis fungoides.

PROGNOSIS.

Kaposi regards the prognosis as absolutely unfavorable, and believes that nothing can be effected, even when the case is taken at the outset, by either excision or any internal medication. The duration of the disease is on the average longer than that of any other form of sarcoma. Hardaway and Köbner have reported cases in which the tumors had disappeared with no recurrence after the lapse of a period of years. In Köbner's case arsenic was given hypodermatically for several months, while Hardaway's case received no treatment.

TREATMENT.

With the exception of Köbner's case, referred to above, arsenic, which has been repeatedly tried on account of its efficacy in other forms allied to this, has given no good results. The intense pain in the hands and feet, when they are greatly swollen and infiltrated, calls for the various soothing ointments, pastes, and washes that we use on inflamed and painful surfaces. The ulcerated surfaces are treated on general medical principles.

Generalized Sarcoma of the Skin.

In addition to the group of cases already described, in which a primary sarcoma, after existing for a longer or shorter time, is followed by a general sarcomatosis, affecting both the skin and the internal organs, there exists another group of cases, not always clearly defined clinically or histologically, in which large numbers of tumors appear over considerable areas of the skin. In a case seen by the writer, a young woman was almost completely covered with closely aggregated nodular lesions, deeply embedded in the subcutaneous tissue and skin, which could not, as a rule, be moved over them, of bluish-red color and not particularly sensitive on pressure. The lymphatic glands were enlarged.

The large number of tumors present is in general a characteristic of this form, although exceptions have been noted. The separate nodules are not large, varying from a pea to a bean in size, although they may sometimes be considerably larger. The edges of the tumors are not very sharply defined from the healthy skin surrounding them. The growths are in some instances painful on pressure; in other instances, not. Certain cases are met with in which it is very difficult to tell whether they belong in this class or with mycosis fungoides. In these cases some of the lesions become elevated and fungous, and may show the same depression in the centre and spontaneous disappearance as do the tumors of mycosis fungoides.

Histologically, these tumors show usually a round or spindle-celled growth. In some cases the appearances may be not unlike those seen in leukæmic tumors and in mycosis fungoides, but many of them have frank sarcomatous characteristics.

DIAGNOSIS.

The diagnosis of this form from mycosis fungoides may in doubtful cases be indicated by the depth of the cellular infiltration, histologically. In mycosis fungoides it is the upper papillary layer of the corium that is primarily and constantly affected; in multiple sarcoma, the deeper layers. The great influence on the progress of this form that arsenic possesses is another means of differentiation from affections that may simulate it.

Prognosis.

The prognosis in this form is much better than in any of those that we have considered, inasmuch as we possess a drug that has unquestioned influence over the disease, and often effects a complete cure.

Treatment.

In 1883, Köbner tried the effect of subcutaneous injections of arsenic in the case of a girl of eight, who was affected with multiple sarcoma, as shown by the microscope. In this instance it was of the spindle-celled variety in the lower layers of the skin. He began by injecting Fowler's solution diluted 1 : 2 with distilled water, of which solution from two and a half to four drops were injected each time. In the course of five months fifty-one injections were made. Then the Fowler's solution was injected in equal parts with water, in the dose of from six to nine drops, into the gluteal muscles, or sometimes into the nodules themselves. There was an improvement noticed in eight weeks, and the tumors finally disappeared, leaving nothing but superficial scars at their site. A year later, there had been no recurrence and the child was perfectly well.

Since then many other cases of successful treatment by means of arsenic have been reported, so that it may be justly said to have a decided influence over this form of sarcoma. Kaposi recommends the arseniate of sodium in 0.02 gm. doses every second day in subcutaneous injections. In a case reported by Shattuck and seen repeatedly by the writer enormous numbers of small tumors were made to disappear in from six to eight months by subcutaneous injections of Fowler's solution.

MALIGNANT GROWTHS ASSOCIATED WITH LEUKÆMIA AND PSEUDOLEUKÆMIA.

Another group of cases exists, in which malignant growths are associated with *leukæmia* and *pseudoleukæmia*. At the present time the pathology of these cases is not well understood. Leukæmia and pseudoleukæmia may run into one another, and both conditions may accompany mycosis fungoides.

Kaposi has described a case which he has named "lymphodermia perniciosa." This form he includes in his chapter on sarcoid tumors, in company with mycosis fungoides and sarcomatosis. It began like a diffuse eczema which resulted gradually in a thickening of the affected parts, upon which nodules, partially ulcerating, developed. The glands and spleen enlarged and leukæmia developed. After death the spleen was found to be greatly enlarged, and there were nodules in the pleura and lungs. Kaposi thinks it will be shown that an etiological relationship exists between this form, mycosis fungoides, and some of the groups of sarcoma. Paltauf and Vidal regard lymphodermia perniciosa as closely connected with mycosis fungoides. Besnier has reported a case which he considers to be similar to that of Kaposi, with whom he agrees as to its distinct clinical nature.

In pseudoleukæmia two varieties of cutaneous lesions have been observed. Arning and Josef have reported cases in which small nodules deeply embedded in the cutis were present, having histologically the structure of leukæmic tumors. These were present in Arning's case, that of a girl of fourteen, on the palate and uvula also. They were characterized by their firm consistence, insensibility, and by the absence of inflammatory appearances at their borders.

The second form of skin lesion that may accompany pseudoleukæmia was first reported by Wagner and later by Josef. There are small nodules resembling clinically the prurigo nodule and Wagner regarded them as of the same nature as true prurigo, while Josef considered them leukæmic growths. In two typical cases of pseudoleukæmia seen by the writer, these nodules were observed. In the first case, there was an enormous hypertrophy of the glands about the neck and a light bronzing of the whole skin accompanied by an excessive general pruritus. The nodules, which bore a strong resemblance to true prurigo nodules, except that they were somewhat larger, were situated on the extensor surfaces of the legs and feet.

In the second case, in which there was also intense pruritus, the nodules were seen upon the arms and legs. A microscopical examination of a nodule excised from the first case showed a corium practically normal, while the epidermis contained a cyst situated in the upper layers of the rete Malpighii, with a wall made up of cornified epithelium. The cyst contained a granular detritus, with some blood and epidermal cells. The horny layer was increased in thickness over the lesion. As the structure of these nodules was precisely similar to that of a mature prurigo nodule, and there was no suggestion of a leukæmic structure, Wagner's view that they are analogous to true prurigo nodules seems justified. The intense pruritus, together with the pigmentation and thickening, is also favorable to this view.

MYCOSIS FUNGOIDES.

This disease, which has received various names according to the different views held as to its pathological nature, was called mycosis fungoides by Alibert, on account of a resemblance which he traced between the exuberant growths upon the skin and certain fungi which break open and pour out an ichorous, bad-smelling mass. Other names that have been given to the affection are granuloma fungoides, inflammatory fungoid neoplasm, multiple sarcoma, lymphadénie cutanée, etc. Totally different clinical appearances may be present at various periods of the disease, so that it has been divided into stages by most writers, following Bazin.

The *first stage* has been called the premycosic, eczematous, or erythematous stage. Rounded, oval, or crescentic, sharply bounded patches of bright red color appear on the trunk, limbs, and face. They are slightly scaling on the surface, and very rarely give rise to any oozing or crusts. They may undergo involution at the centre, thus giving rise to circinate and gyrate figures, or they may coalesce, forming extensive red and scaling areas. There is very marked pruritus, and in most instances the affection cannot be differentiated at the outset from a squamous eczema. These eczematous patches may come and go for a period of years before the affection reaches its second stage. In some instances the erythematous patches are œdematous, giving them an urticarial appearance. Instances are on record in which the affection has begun quite suddenly with fever and rheumatoid symptoms. Sometimes the eczematous plaques appear only in summer for a succession of years before a further stage is reached.

The *second stage* is reached when the plaques become infiltrated and raised, the circinate and gyrate figures standing out sharply. Papules and nodules begin to appear, both in the normal skin and on the eczematous plaques. These nodules are hard, round, pale red in color, from the size of a pea to that of a bean and larger, and sharply bounded. Interspersed with them are often seen wheal-like elevations and patches, which have undergone involution in the centre, so that circinate, serpiginous, and gyrate figures are produced. The nodular lesions may undergo this same involution, and hard, sharply raised rings of infiltration may be found. These infiltrations may appear on any part of the body, but the most extensive areas are usually situated on the trunk. They may persist, or disappear rapidly, leaving pigmented areas behind or a superficial atrophy; while new lesions of a similar character appear at other points. This stage has been called by Bazin the "périodo lichenoide"; by others, the infiltrated stage.

The *third stage* is the tumor or fungoid stage. The prominent features of the tumors are their sudden and quick growth, and their rapid involution, either spontaneously or as a result of treatment, so that nothing is left in their place but a pigmented patch. These tumors vary from the size of a small nut to huge growths as large as the two fists. They may grow immediately from the eczematous plaques, and in this case the second stage is skipped; they may result from the increase in size of the nodules and infiltrations; or lastly, they may appear suddenly without either a preceding eczematous or a lichenoid stage. The last variety has been called "mycosis fungoides d'emblée."

The tumors are red, nodular, and sometimes lobulated, or they may be constricted at the base, so that fungous appearances are produced and some of the growths have been compared to tomatoes. They may break down into necrotic fungous ulcers, which are either superficial or deep and are often covered with papillary outgrowths. They may occur on any part of the body and as a rarity upon the mucous membrane of the mouth and throat. In a case seen by the writer in which the body was covered with innumerable growths, there were two growths upon the scalp of the shape and appearance of large potatoes, which they strongly resembled. Interspersed among these fungoid tumors and papillary ulcerations are usually areas of infiltrated skin, of the type of the second or infiltrated stage, so that the second and third stages may be represented at the same time.

A remarkable characteristic of these tumors is their spontaneous involution, leaving the integument at their site in an almost normal condition. In a case of Bazin's, in which the scalp was the seat of the tumors, they disappeared without even a resulting alopecia. Sometimes the subjects of this disease remain for a period of several years without marked impairment of the general health. At other times there are progressive failure and debility from the outset. In the later stages, when the tumors have begun to ulcerate and to break down, marasmus sets in and death follows at a longer or shorter interval. Fever is rare in this disease, except in connection with a septic condition of the ulcerated surfaces. The glandular system is not affected as a rule, although there are cases in which there is considerable enlargement.

PATHOLOGY AND HISTOLOGY.

There has been a great variety of opinions as to the nature of this disease, based upon varying interpretations of the histological appearances, and its position has not as yet been definitely settled. Köbner and Virchow believed that it was to be classed with the granulation tumors, and hence it came to be regarded as a chronic infectious disease by many authorities. It was in this sense that the name granuloma fungoides came into use. This theory was espoused by Ledermann, Tilden, Neisser, Doutrelepont, and others. Paltauf has shown that the cell growth in mycosis fungoides has few of the characteristics of a true granulation tissue. In the cases examined by him there was a marked absence of all signs of emigration, such as the heaping up of polynuclear round cells about the vessels. This absence was observed even where there was active cell proliferation, as shown by the presence of numerous karyokinetic figures. There was also no new formation of vessels to any extent; the most that could be determined was an increase in size in some of the preexisting vessels of the papillæ. Another characteristic of granulation tissue is the development of its elements into embryonic connective tissue, and when this does not occur there is an early resolution. Neither occurs in the case of mycosis fungoides.

Many analogies have been drawn, from the clinical appearances and course, between mycosis fungoides and leprosy and other infectious granulomata, but these are not of great weight. The attempts to discover a microorganism as a causative agent have been thus far totally unsuccessful, although many claims have been advanced. Micrococci have been described by Rindfleisch, Hochsinger and Schiff, and Stelwagon. In some of these cases, examined before bacteriological methods had reached their present development, the microorganisms were undoubtedly due to a complication of the disease with septicæmia, and represented the ordinary microbes of sepsis. None of them possesses any claim to be regarded as specific. Many eminent authorities have repeatedly examined the tissue at a time when the general condition was not affected, with a negative result so far as the presence of bacteria was concerned.

A further analogy with parasitic skin affections has been adduced from the circinate and serpiginous arrangement of the nodules and infiltrations of mycosis fungoides, which exhibit a resolution in the centre, with advancement of the periphery—appearances which are regarded as more or less characteristic of a local infectious process. It has not been proved, however, that this arrangement is found solely in infectious processes. It is seen in psoriasis, of the parasitic nature of which there is no conclusive evidence, and it is to be remembered further that it is possible that anatomical conditions, such as the arrangement of the lymph channels, may be equally well advanced as its cause.

Another theory, espoused especially by French writers, is that mycosis fungoides is a lymphatic new formation, and the name lymphadénie cutanée has been given to it by many. This theory was first advanced by Gillot-Ranvier, and was accepted by Bazin and numerous other French writers, including many of the present day. There are many good reasons to be given for this theory. It would seem that certain cases which have all the clinical characteristics of mycosis fungoides resemble a lymphatic neoplasm much more closely in their histological characteristics than do others, and that many of those who have advocated this theory have had this class of cases before them. In such cases we find very small and equal-sized round cells with a fine reticulum, which bear a close resemblance to lymphatic formations. And yet the fact that it has been shown that in many cases of mycosis fungoides the round cells are derived from connective-tissue cells, and that the reticulum has its origin in the original connective-tissue fibrils, makes this view exceedingly improbable, if it does not definitely disprove it.

Another set of writers, relying on the definition of sarcoma as a connective-tissue tumor, which is characterized by a predominating development of the cellular elements, regard the tumors of mycosis fungoides as of a sarcomatous nature. Kaposi has always been an earnest advocate of this theory. In the later editions of his text-book he has established a class of so-called sarcoid tumors, in which he includes both the various forms of cutaneous sarcomata and mycosis fungoides. With regard to mycosis fungoides, there are certainly numerous points of resemblance with sarcoma. We have a preponderance of young, partially developed cells, with a disappearance of connective-tissue bundles, and it has also been shown that the cells of the tumors are derived from the connective-tissue cells. On the other hand, the spontaneous disappearance of many of these tumors is in direct contradiction to the classical conception of sarcoma, and Paltauf regards this characteristic as an argument of sufficient weight to warrant the rejection of the theory. If, however, we exclude mycosis fungoides from the sarcomata on this ground we must also exclude the multiple idiopathic pigmented sarcoma of Kaposi, one of the attributes of which is spontaneous involution, but which on every other ground seems entitled to a place with the sarcomata, and its histological structure is entirely typical of the latter class.

Other reasons that have been urged against the theory that mycosis fungoides is a form of sarcomatosis are the fact that the tumors appear as symptoms in the course of a disease, and that they have no central growth, but arise as diffuse infiltrations oftentimes. Nevertheless in my own opinion there are too many analogies with sarcomata to warrant us, in the present doubtful state of our knowledge of the pathology, in excluding the possibility of a close relationship between the different forms of cutaneous sarcomata and mycosis fungoides. I have observed several cases in which it was difficult if not impossible to determine whether the affection should be classed with the sarcomata or with mycosis fungoides. In one instance, that of a man of fifty-two, the affection began by an increase in size of the testicles, and the cutaneous lesions did not appear until several weeks later. These consisted of nodules varying in size from a bean to an egg, which were firm, bluish-red, and somewhat elevated. Some of them were umbilicated or slightly ulcerated. There were also erythematous and urticarial infiltrations, which were sharply bounded and had assumed circinate and serpiginous forms from central involution and peripheral extension—appearances that are quite typical of mycosis fungoides. Many of the tumors had disappeared spontaneously while others had made their appearance. At the autopsy the scrotum was found to be enlarged to the size of two fists on account of a new formation in each testis, which was precisely similar histologically to the tumors of the skin. Similar neoplasms were found in the kidneys and mesocolon. These were made up of very small round cells, which were enclosed in the meshes of a delicate reticulum and rather deeply situated, the papillary layer not being involved. There were also a few irregular and fusiform cells.

In this case the lesions were similar to those of mycosis fungoides histologically, with the exception that the papillary layer of the corium was not involved, and the appearances were less superficial. On the other hand the affection of the testicles, kidney, and mesocolon is a rare occurrence in mycosis fungoides of the pure type. The affection of the testicles before the appearance of any cutaneous lesions, the absence of the so-called premycosic stage, and the failure of the tumors to ulcerate and assume papillomatous and fungous appearances, are further points of variance from mycosis fungoides.

In another case seen by me, that of a French Canadian, forty-eight years of age, the first appearances had been an infiltration and thickening of the nostril and bridge of the nose. Several months later the right testicle became swollen, and a tumor appeared on the right external malleolus. Subsequent to these appearances came the cutaneous lesions, which consisted of nodules varying in size from a chestnut to an English walnut, bluish-red in color, and seated chiefly on the lower extremities. In some of them involution had taken place in the centre, giving rise to umbilicated appearances. There was a small lesion on the conjunctiva. None of the tumors had disappeared spontaneously. There was a slight improvement under the use of arsenic subcutaneously, but the patient failed rapidly and died. Unfortunately, there was no autopsy, but the histological examination of the nodules agreed perfectly with that in the case just referred to.

This case furnishes another instance of what may be called transitional forms between sarcomatosis and mycosis fungoides, although here there are more of the attributes of the latter affection than of the former.

Lastly Paltauf is inclined to include mycosis fungoides under the anomalies of vegetation proposed by Kundrat, which comprises pseudoleukæmia and certain forms of lymphosarcoma. This rather vague conception is that of a class of diseases that owe their origin, not to a special cause, but to an abnormal reaction of the individual, and are dependent upon an abnormal vegetation.

DIAGNOSIS.

There are not many diseases that could be mistaken for mycosis fungoides, when well advanced, but at times there may be considerable difficulty in diagnosis, especially at the outset. There may sometimes be a state of generalized erythema, called by the French "érythrodermie," which may precede by many years the appearance of the tumors, while in other cases it may succeed them. In the former case it may be very difficult if not impossible to foretell the future development of the disease, and the "érythrodermie" may be taken for a pityriasis rubra, a scarlatiniform erythema or dermatitis, or an exfoliative dermatitis. According to Besnier and Hallopeau a mycosic erythrodermia may be differentiated by the thickening of the skin, its distention so that it may be readily picked up in folds, the absence of all desquamation, the presence of intense pruritus, and a considerable increase in the size of the lymphatic glands. This condition of is very apt to undergo complete or partial involution, leaving well-defined pigment stains.

It is usually impossible at the very outset, when the disease has not progressed beyond the eczematous stage, to differentiate it from an ordinary chronic and recurrent eczema. Points of distinction from the latter affection are the greater infiltration of the patches, their sharp outline and tendency in places to resolution in the centre, and the presence in some instances intercurrently with the eczematous appearance of erythematous, urticarial, and nodular lesions which form circinate and serpiginous figures.

In some instances there may be much similarity between the lesions of mycosis fungoides and those of leprosy, when the affection has progressed to the lichenoid and infiltrated stage. The absence of anæsthesia and of other characteristic symptoms of leprosy will usually exclude the latter disease, even if it is not possible to obtain a bit of tissue for examination. The presence or absence of the bacilli of leprosy will determine the question definitely. The similarity between mycosis fungoides and sarcomatosis in many instances has been referred to under the head of pathology. It may be very difficult to determine which of the affections we are dealing with, and the microscope cannot always be relied upon to settle the question.

PROGNOSIS.

The prognosis of this disease is very unfavorable. One case has been reported by Köbner, cured by arsenic, but none since. A spontaneous recovery after erysipelas has also been recorded by Bazin.

TREATMENT.

Arsenic is usually tried, both internally and hypodermatically, on the strength of Köbner's reported case of cure. The benefit, if any, is of a temporary character; otherwise the treatment is symptomatic. Antiseptics should be used in the later ulcerative stages, as death has sometimes occurred from septicæmia.

MALIGNANT DISEASES OF THE FEMALE ORGANS OF GENERATION.

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MALIGNANT DISEASES OF THE FEMALE ORGANS OF GENERATION.

THE VULVA.

The malignant diseases of the vulva are carcinoma and sarcoma. These affections are rarely primary, but usually are an extension of malignant lesions from the vagina or uterus. The investigations of Winckel and Gurtl show that they occur as primary formations in about one per cent. of all cases of malignant diseases. Pozzi states that in his opinion this proportion is too great, and he thinks it is probable that many of the cases reported were secondary in their origin.

The most common form of cancer of the vulva, epithelioma, does not differ histologically from the same disease in the uterus, and is more particularly described in the section on cancer of that organ.

Symptoms.

Carcinoma may originate in different parts of the vulva, but usually begins as small, round, or irregular nodules on the inner surface of the labia majora or in the groove between the labia majora and minora. The nodules are covered with several layers of scaly epithelium which is lost when ulceration begins. In the incipiency these nodules grow slowly, are painless, and produce no symptoms except some slight pruritus. Their presence may remain for some time unnoticed, and the nodules may combine, enlarge, and invade the surrounding structures before ulceration occurs. When excoriation follows from friction there is pain together with serous or bloody discharge. Sooner or later ulceration occurs and further infiltration and hardening of the adjacent tissues ensue.

The margins of the ulcers, when formed, are irregular and raised. New papillæ or granulations spring up through the raw surface and may attain considerable size. The ulcer is covered with a seropurulent, ichorous, fetid discharge. The disease rarely extends to the opposite side.

After ulceration has existed a short time the inguinal glands become involved, and about this period the disease progresses more rapidly and extends into the deeper tissues. The nymphæ and clitoris may become involved, and the disease may finally extend into the vaginal walls. Pruritus, increasing with the progress of the disease, is always present. Severe hemorrhages are rare. Pain may be absent throughout the entire course of the disease, or may be a persistent symptom. Death usually occurs in two or three years after ulceration sets in and is the result of gradual exhaustion, due to the general depreciation incident to carcinomatous growths and to the accompanying toxæmia. The end is occasionally hastened by some complication, as phlebitis or pleurisy.

Sarcoma of the vulva is very rare. In 483 cases of sarcoma found among 11,140 cases of tumors of all kinds, not one case of sarcoma of the vulva was reported (Winckel). The different varieties of this disease may be present, but the two most common types are melanosarcoma and myosarcoma. The disease occurs more frequently in the young, differing from carcinoma in this respect. The growth usually begins in the labia majora, but it may originate in any portion of the vulva. The symptoms for some time are not severe except when excoriation, induced by friction in walking, or ulceration sets in. When situated about the urethra, micturition may be rendered difficult. This also is the case in carcinomatous infiltration around the urethra, producing what is known as the periurethral variety of cancer.

ETIOLOGY.

The etiology of malignant growths of the vulva is but little known. Carcinoma is most frequent between forty and sixty years of age. Heredity appears to have no influence. Certain injuries, as blows and falls, are said to predispose, as does the continuous rubbing and scratching of the parts for the relief of a pruritus. It is stated by Pozzi that psoriasis favors the development of epithelioma.

DIAGNOSIS.

Syphilis and lupus may be mistaken for epithelioma in the early stage, but the history is different and the symptoms are unlike. A chancre commences either as an abrasion or a slightly projecting papule with little secretion or discharge. The inguinal glands are quickly involved and the constitutional symptoms soon manifest themselves. A chancroid appears as an acute ulceration without induration. The edges of a chancroid are sharply cut and perpendicular.

In lupus, ulceration and cicatrization are going on at the same time—destruction and repair. Epithelioma is more localized, with greater density of the tissues, followed sooner or later by enlargement of the inguinal glands. The pain in epithelioma is lancinating; lupus is almost painless, nor is the discharge offensive in the latter.

TREATMENT.

Total removal of the disease is the only method which holds out any prospect of a cure. This should be done by an early and complete excision—extending the cut well into the healthy tissue and bringing the surfaces together, if possible, by deep sutures. If the urethra is implicated care must be taken to restore its calibre, while if the inguinal glands are involved they also should be removed. The galvano- or thermocautery may be used for removing the growth, and is preferred by some gynecologists. Caustics have been generally abandoned by the profession as their application is painful and the results are uncertain. When the disease has progressed beyond surgical relief, palliative measures are to be adopted. The symptoms which cause most discomfort are the intense pruritus, fetid discharge, and irritation of the surrounding parts. These are to be treated by removal of as much of the growth as possible with the cautery or curette and the frequent application of antiseptic washes. Borated vaseline applied to the thigh will afford relief to the erythema caused by the fetid discharge. The application of iodoform and charcoal, packing them in the ulceration with gauze, is useful. The application of protonuclein and carbide of calcium may be tried, but local cleanliness and anodynes are to be chiefly relied upon when surgical interference is not warranted.

THE VAGINA.

The malignant diseases of the vagina are sarcoma and epithelioma, the latter being papillary, infiltrated, or nodular in form.

Sarcoma.

Sarcoma of the vagina occurs either as a circumscribed tumor resembling a fibroid and known as a fibrosarcoma, or as a diffuse sarcomatous infiltration of the mucous membrane. Sarcoma is very rare and is usually a primary growth. It occurs at any age—sometimes in early childhood. The site in children is most frequently the anterior wall, in adults the posterior. The circumscribed form develops more slowly than the infiltrated, and ulceration occurs later in the disease. The inguinal glands rarely become involved, and then only in the later stages.

The *symptoms* are insignificant in the beginning. An irregular hemorrhage after coition or on some exertion is one of the first; leucorrhœal discharge, afterward becoming sanious and fetid when ulceration takes place. Pain and discomfort incident to pressure, with a sense of bearing down, are present in the fibrosarcomatous variety. If the growth is situated on the anterior wall dysuria from pressure occurs earlier than if it is on the posterior wall. The disease may extend through the vaginal walls and produce rectal or vesical fistulæ.

The *diagnosis* can be made with certainty only by the aid of the microscope.

The *prognosis* is exceedingly bad, but is more favorable in the circumscribed than in the diffuse variety on account of the greater possibility of complete removal.

Treatment consists in complete and early removal by the knife before ulceration or glandular involvement has ensued. The diffuse form may be kept in check by repeated curetting and cauterization with the thermo- or galvanocautery; or chloride of zinc may be applied as in cancer of the uterus.

Cancer.

Primary cancer of the vagina is very rare, but secondary involvement is quite common. It may be an extension by continuity from some other diseased organ, especially the cervix uteri, or it may be associated with cancer of the rectum or vulva. While carcinoma is more common than sarcoma, Martin has found but four cases of primary origin in five thousand cancer patients. It occurs in two forms; first, as a papillomatous growth, usually on the posterior wall, with a broad infiltrated base, or as nodules quickly becoming confluent, giving the appearance of an infiltration of the vaginal wall, either annular in shape or extending over a large area. The growth is sometimes localized about the urethra, producing what is known as the periurethral form of cancer.

Etiology.—There is little known concerning the etiology. According to the statistics of Küstner it is more frequent between the ages of thirty and forty. Child-bearing is not a predisposing cause as it is of cancer of the cervix.

Symptoms.—The course of the disease is rapid. Ulceration soon appears, while extensive infiltration into the surrounding tissues occurs. As a result of the destruction of tissue, perforation into the bladder or rectum frequently follows. Rectovaginal fistula is more common on account of the usual site of the neoplasm. Extension through the lymphatics and involvement of the pelvic connective tissue and of the inguinal canals are frequent complications. The symptoms are like those of cancer of the cervix, viz., irregular discharge of blood after coition or straining at stool, slight pruritus, increasing in intensity as the disease progresses; mucopurulent discharge, later becoming sanious, watery, fetid, and irritating; pain and the symptoms incident to obstruction or involvement of the adjoining organs, the bladder and rectum.

Diagnosis.—Carcinoma may be mistaken for benign papilloma. It will be noticed in the latter that the base is not fixed or infiltrated as in the former. The hard, fixed base, the friability of the tissue, the hemorrhage caused by touch, and later the watery ichorous discharge will make the diagnosis almost certain. On account of the rarity of primary carcinoma of the vagina a careful examination of the neighboring organs, from which it may have spread, should invariably be made.

The *prognosis* is unfavorable. Patients rarely apply for aid before the disease is well advanced and it is too late for successful removal. If not removed before ulceration takes place it is almost certain to recur.

Treatment.—Though complete extirpation of the neoplasm is unsatisfactory still it offers the best chances for a cure or prolongation of life. When the growth is circumscribed with enough healthy tissue around to warrant complete removal, this should be done, the edges being brought together with sutures. On account of the elasticity of the vaginal walls it is possible after extensive excision thus to reunite the edges; but if the loss of tissue be too great to admit of primary union the surface may be cauterized with a thermo- or galvanocautery and packed with gauze. This should be removed in forty-eight hours and be followed by antiseptic douches. In some cases it may be necessary to make a transverse perineal section and dissect up the posterior wall as recommended by Pozzi and Olshausen. In inoperable cases the removal of the cancerous mass as far as possible by the curette or cautery, or both combined, is the best means of controlling the hemorrhage and discharge. The application of caustics or the cautery should be made with care because of the liability of opening into the bladder, rectum, or peritoneal cavity. Frequent cleansing douches of creolin, permanganate of potassium, peroxide of hydrogen, and applications or suppositories of iodoform and charcoal, protonuclein, aristol, or carbide of calcium may be used. Moderate hemorrhage will usually be controlled by applying a five or ten per cent. solution of antipyrin, or, if alarming, by packing with gauze saturated with a solution of alum or tincture of iron. Pain should be relieved by narcotics. They should be given freely as the suffering increases,

THE UTERUS.

Cancer.

Aside from the exciting causes supposed to produce carcinoma of the uterus, there are many other conditions which increase the possibilities of its development. A knowledge of these is indispensable to the intelligent study, relief, and prevention of this disease.

ETIOLOGY.

Carcinoma is more often found in women because of the frequency with which the disease affects the uterus. Simpson showed that of 80,000 deaths from cancer, over 61,000 occurred in women. His statistics proved that the proportion in the sexes was about equal at puberty, but from that age on the ratio grew until at from forty-five to fifty-five the proportion of women to men affected was three and one-half to one. The predominance of uterine carcinoma has been demonstrated by Schroeder, who showed that in 19,666 cases of carcinoma in women 6,548 were of the uterus. According to the statistics of Emmet, Glätter, Winckel, Hofmeier, Schroeder, E. Wagner, Gusserow, Scanzoni, and others, between two per cent. and three per cent. of all gynecological cases are carcinoma of the uterus. Winckel places the percentage as high as 3.5.

Predisposing Causes.

Age.—Carcinoma most frequently occurs between thirty and seventy years of age. While some of the cases reported in patients under thirty are undoubtedly carcinoma, yet the majority are sarcoma. Hofmeier, in an article upon the subject, gives some interesting statistics. Of 812 cases the body was first involved in but 28 cases; the portio vaginalis in 181; and the cervix in 236. In 367 cases the primary seat was not known. The average age in carcinoma of the portio was 42 years; in carcinoma of the cervix 47 years; in carcinoma of the body 54.5 years. These figures substantiate the well-known fact that two-thirds of the cases occur between the ages of forty and sixty.

Race.—Uterine carcinoma is comparatively rare in the colored race. It is most common among the Caucasians. "This fact seems to imply that persons more highly organized intellectually and morally are rather more subject to this scourge than those who are more callous or less intellectual or imaginative" (Sinclair).

Social Class.—By far the larger number of these cases occur among the lower classes. Müller found in an analysis of five hundred and seventy-seven cases that they were all among the laboring class. When we remember what these women have to undergo from extensive and usually neglected injuries to the uterus and vagina; constant and excessive work connected with domestic duties, or to provide for themselves and dependents; repeated pregnancies; protracted periods of lactation; the cares of a large family; lack of proper nourishment and sufficient clothing; too often the excessive use of alcohol; mental depression from want, abuse, and worry—these and many other accompaniments of their lives cannot fail to impress the gynecologist as potent factors concerned in the prevalence of this disease. Sinclair says: "We may assume that cancer may be banished by social ameliorations which will raise the present existing cancer-producing class to the higher level of the present existing immune."

Parturition.—Repeated pregnancies are considered by many writers as a predisposing cause. Hofmeier reports that of 849 cancer patients who had borne children, 100 had had one child, 667 had an average of 5.8 pregnancies, and 76 had over ten pregnancies. Pozzi inclines to the belief that repeated pregnancies act only by the attendant extensive cervical lacerations and inflammations. In from eleven to twenty per cent. of all cases of uterine cancer, according to different observers, the disease develops soon after confinement. It has also been shown by Hofmeier that those carcinomata developing so soon after parturition are of a more malignant nature, running a more rapidly fatal course. This he attributes to the increased number of lymphatics throughout the uterus. In all probability the only effect which repeated parturition has upon the occurrence of cancer is through the diminished vitality and lowered resistance of the uterine tissue, together with the accompanying lacerations of the cervix, where are found newly formed scar tissue, ulcerations, and erosions—abnormal conditions which predispose to the development of a lower grade or a typical form of tissue.

Heredity.—Despite the many striking cases reported or from time to time observed, the theory of the hereditary nature of cancer has gradually lost ground for lack of scientific confirmation. Parker reported that in 7.6 per cent. of the cases collected by him there was a history of carcinoma in some ancestor or member of the family. Other writers place the number as high as 13 per cent. The loose application of the term cancer undoubtedly can be held accountable for such a high percentage at this last. When we see the success (?) of so many "cancer cures" advertised, the unreliability of ordinary information on this score is apparent. With the present exact methods of diagnosis, and with a closer scrutiny of the cases, statistics could now be gathered which would be more reliable.

Gonorrhœal Infection.—That gonorrhœa may predispose to the development of cancer is considered very likely by Winckel, who has been impressed by this fact after treating several cases of parametric exudation and carcinoma rapidly following gonorrhœal infection. There are as good grounds for considering that the metritis of gonorrhœal infection is a predisposing factor in carcinoma of the fundus as that lacerations or erosions predispose to cancer of the cervix.

Exciting Causes.

The specific or exciting cause of carcinoma is as yet undetermined. In the last few years research has tended strongly to remove it from the list of tumors arising solely from abnormal or eccentric development of either embryonal or mature cells and placed it among those diseases due to some form of parasitic development. Notwithstanding this fact other theories are widely accepted as worthy of consideration.

The embryonal origin of carcinoma, the theory of Cohnheim, has received much attention and support. It is that tumors are the result of imperfect congenital embryonal development. Certain groups of cells are supposed, during fœtal life, to be in excess of what is required and become useless or displaced, or for some reason fail to develop. At some future time under proper stimulus these latent cells commence to develop and multiply with an activity characteristic of embryonal cells, and not being limited or restrained by the influences which at the time of their proper growth would have regulated their development, result in an excessive production or tumor. In substantiation of Cohnheim's theory may be quoted the hereditary nature of cancers; their atypical growth; the fact that they are not subject to those nervous mechanisms which render the metabolism of the part subservient to the good of the whole; and that they are generally located at points where considerable complexity of tissue pertains, rendering errors of development more likely. This theory, attractive as it is, lacks actual confirmation. These resting groups of embryonal cells have not as yet been demonstrated, a point which Cohnheim explains is due to their minute size and resemblance to leucocytes.

Various animal and vegetable parasites have been studied and described in their possible etiological relation to carcinoma. E. Ziegler states that in cases in which the presence of protozoa has been demonstrated, the growths have been those which could not be considered genuine cancers. The bodies in the cancer cells which have been taken for animal parasites, according to Ziegler, are partly products of retrograde metamorphosis; partly products resulting from the reception of leucocytes into the epithelial cells, followed by a degeneration and disintegration of the leucocytes; partly products of a nuclear division which is pathological or in some way distorted; and partly products of altered cell division or of the inclusion of one cancer cell by another. Their presence cannot be entirely disproved even by this sweeping statement by Ziegler. Other and excellent observers continue to describe animal parasites in cancer cells, maintaining that they can be readily stained in properly hardened sections and giving detailed descriptions of their morphology. They point to the epithelial proliferations found in the liver, bile-ducts, kidneys, and other organs, due to the action of certain protozoa, as examples of the power of these parasites to produce new growths, and claim that the presence of these bodies in cancer cells is strongly suggestive of their etiological relation to cancer.

In the study of the vegetable parasites considerable advance has apparently been made. The earlier investigators endeavored to isolate a specific bacterium, but failed, and only when attention was directed to certain of the fungi were there important developments. In 1894 O. Busse described certain yeast fungi which he found in malignant tumors. One year later Sanfelice and Roncali published accounts of their investigations. They had detected fungi in carcinoma, had cultivated them, and had produced by inoculation tumors which resembled carcinoma, and which were accompanied by metastases throughout the body; and from these tumors they had isolated specimens of the fungus. The inference to be drawn from the results of these and other investigators is that certain members of the fungus class are among the exciting causes of carcinoma, if not the sole cause. The fungi studied are of the class known as blastomycetæ, noted as that to which the various yeast plants belong. They reproduce and multiply by the process known as budding, in which the young cell appears as an outgrowth or leaf on the parent cell. They are easily cultivated upon acid media (bacteria usually requiring an alkaline or neutral one), and produce the characteristic fermentative reactions. They are found in the juices of the periphery of the tumor, their presence in the centre being variable. This peripheral location is suggestive of the relation of the plant to the growth of the tumor.

Cancer of the Cervix Uteri.

Pathological Anatomy.

Carcinoma of the cervix is the most common form of uterine cancer. About ninety-seven per cent. of all cases of cancer of the uterus are cervical. The former classification of scirrhus, encephaloid, and colloid is now abandoned by most pathologists. One carcinoma may present two or all of these forms in different parts or at different phases of its development.

Carcinomata of the cervix are divided into two classes: (1) the papillary and (2) the nodular variety.

Papillary Variety (Fungoid, Cancroid, Cauliflower, or Vegetating Form).—This occurs either as flat, granular elevations, or long villous processes. It may be localized for some time, or may rapidly extend, involving and occupying the former place of the cervix. These fungosities are composed of loops of blood-vessels, surrounded by layers of rapidly proliferating epithelioid cancer cells. This is a frequent source of hemorrhage in these cases, due to the impeded circulation following the rapid proliferation of the cells and the degeneration of the intima of the capillary loops. It arises from the pavement epithelium and glandular structure about the cervical lips, and usually grows towards the vagina, supposedly because of the different form of epithelial cells in the cervical canal. The fungoid growth is commonly located on one lip.

Nodular Variety (Submucous, Infiltrated, or Ulcerating Form).—This commences as one or more nodules or infiltration masses situated in the substance of the cervix. As these masses grow they approach the surface and cause ulceration of the overlying mucous membrane. The different masses coalesce, and the cut section presents a whitish, glistening appearance, with included islands of normal tissue. The ulcers spread and coalesce as the growth enlarges, and their margins are preceded by an indurated ridge, marking the advancing proliferation of the cancer cells. If the nodules are superficial, ulceration follows quickly and destruction of the cervix usually results. But when the nodules are more deeply situated and develop more slowly, the cervix is usually greatly enlarged and elongated and very hard.

In some cases the mucous membrane or submucosa of the cervical canal is the starting-point of the disease. Here the tendency is to respect the os externum, and the growth is towards the body or the junction of cervix and vagina. A considerable destruction of tissue and cavity formation may result while the os externum appears normal, the growth being funnel-shaped, with the base extending towards the body. The walls of these cavities are ragged, lined with fragments of disintegrating tissue, show more or less induration and irregularity, bleed readily, and are covered with a thick, brownish, grumous discharge.

The ulceration of the mucous membrane is brought about by interference with its blood supply. The blood-vessels are included in the nodules, and the lumen is gradually lessened until sloughing results. The ulcers vary in shape and depth; sometimes they are circular, usually they are irregular in outline. When recent, the base is covered with rough necrotic shreds, but when far advanced it is more smooth and seems to consist of dense connective tissue.

Histology.

A carcinoma is an epithelial tumor. The term epithelial does not imply that it is made up of a specific form of cell, but that it lacks intercellular substance. The cells are derived from the epiblast or hypoblast.

The characteristic formation of carcinoma is the group of so-called cancer cells surrounded by connective tissue. These cells justify their comparison to epithelial cells by their appearance. They are large, and contain large bladder-like nuclei. The nuclei are usually single, but two or three are often found, and in tumors rich in cells (the so-called "medullary cancer") many more are seen. The cells are noted for their various shapes, often corresponding to the epithelium of the tissue in which they are growing; but frequently their polymorphy is due to pressure effects caused by the rapid growth of the tumor. These cells undergo rapid degenerative changes, and at times under the microscope free nuclei are noticed throughout the tissue. The cells lie in a network of stroma (the predominance of which constitutes the "scirrhus" cancer), which at first may be normal connective tissue, but later increases as the tumor develops. This stroma forms alveoli in which the groups of cells rest, but between the individual cells no fibres are found. It contains blood-vessels, which, however, do not come in contact with the cells. Throughout the stroma are noticed leucocytes, which may pass into the alveoli and among the cancer cells.

The cells usually spread in the connective tissue along the lymph channels and spaces, either by the action of the lymph stream or by cellular motion, and this explains the accompanying glandular infection.

In carcinomata arising from the vaginal portion of the cervix the development is characterized by the formation of nests of cells, derived either from the stratified epithelium or the margin of the gland ducts. The growth is histologically a characteristic "epithelioma." Here are found the so-called "epithelial pearls." According to Pozzi, true stratified epitheliomata are rare.

Cylindrical or glandular cancer in its incipiency resembles an adenoma, showing many newly formed tubules lined with a single layer of cylindrical epithelium. More rapid proliferation usually follows, and the newly formed tubules become lined with many layers of epithelial cells until they are completely filled by them. To this growth is given the name of adenocarcinoma by some writers. They are differentiated from true adenoma by their atypical development and the invasion of the surrounding tissue by cancer nests. These cancers, showing this typical cell proliferation, and the invading nests, are typical carcinomata, or, as Pozzi calls them, "atypical epitheliomata." In this form colloid degeneration is prone to occur. Microscopically the induration about the edge of the ulcer is due to the invasion of rows or groups of cancer cells, the migration of leucocytes into the tissues, and the infiltration of the tissues with serum. The last two are the result of nature's effort to wall off the ulcer from the surrounding healthy tissue.

Extension.

Carcinoma of the cervix and vaginal portion extends to the vault in eighty per cent. of all cases (Winckel). Extension from the cervix to the body occurs late, as does extension from the body to the cervix.

After involvement of the vagina the disease spreads into the muscular coat of the bladder or rectum, then into the mucous membrane, and is not infrequently followed by perforation. In other instances it may pass down the vagina and involve the external genitals. The pelvic glands commonly become diseased. This, together with deposits in the broad ligaments and the connective tissue about the sac of Douglas, not infrequently produces fixation of the uterus.

The ureters may be interfered with either by extension up the mucous membrane of the bladder to their orifices, or by primary extension up the sides of the cervix, or down from the body. The result is either a ureterovaginal fistula or an occlusion of the ureters with dilatation, and finally hydronephrosis. Lancereaux states that renal disease is constant in advanced cases, and indeed its frequency is well known. In cases in which occlusion of the ureters has not yet occurred ureteritis may be set up, and in a small percentage of cases pyelonephritis has been reported. The sacral plexus and its branches and large venous trunks may be included in the growth, resulting in intense pain and œdema. In rare instances involvement of the bony pelvis has been reported. From the body of the uterus the growth may pass into the tubes and even involve the ovaries, which are found diseased in eighteen per cent. of the cases. The tendency in cancer of the body is usually to involve the peritoneum, and in this connection we find the peritoneum throwing out adhesions in an endeavor to limit the growth.

Metastasis may occur in other parts of the body, as the kidney, liver, lungs, stomach, gall-bladder, and dura mater; but it is exceptional. Gusserow reports 44 cases of metastasis out of 283 cases. In

166 cases reported by another observer, there were 45 cases with metastatic deposits. These distant metastases develop from cancer cells transplanted by the lymph, or exceptionally the blood streams, while the extension to neighboring parts is by the infiltration of chains of cancer cells.

SYMPTOMS.

Unfortunately the onset of the disease is so insidious that the patient usually feels and appears in good health until the growth is far advanced. For this reason we rarely have an opportunity to observe the initial symptoms of cancer of the cervix. The first symptom that attracts attention is a slight discharge of blood at irregular periods, after coitus, some exertion, or straining at stool. If occurring about or after the menopause, it is usually attributed to that condition and welcomed by the patient as a return of her menses. The bleeding at first is not probably due to ulceration, but to congestion incident to the presence of the neoplasm, and has been likened by Pozzi to hæmoptysis in the early stage of tuberculosis. Preceding the hemorrhage, or associated with it, there is frequently a leucorrhœal discharge, which may be profuse, glairy, or mucopurulent, accompanied by some itching of the vulva. There is often a sense of weight or pressure, a frequent desire to urinate, and certain reflex phenomena of the digestive and nervous systems, similar to what is seen in chronic metritis. Following this, the second characteristic symptom appears as a foul discharge. At first the discharge may be serous and devoid of odor. This is especially so in the papillomatous variety, which in the early stage is profuse, tenacious, slimy, afterwards becoming purulent, brownish-red, and offensive. In the other forms the discharge is serous, and later assumes a dirty grayish or brownish appearance. It is very offensive, profuse, and acrid, producing excoriation, erythema, and an intense pruritus of the external genitals and surrounding parts.

Pain as a prominent symptom is not present in the early stages, though there may be slight pains referred to any part of the pelvis, as is seen in chronic metritis. In the early stages of carcinoma of the cervix, when the vaginal portion alone is affected, there is little pain. It increases with the invasion of the tissues around the uterus. It is at first sacral, later in the region of the kidneys or hypogastrium, then in the thigh and extending down the limbs. In about five per cent. of the cases there is no pain present at all. When the broad ligaments and peritoneum are involved, the symptoms are like those of pelvic peritonitis. The pain at first is darting or shooting in character; later is boring, lancinating, or gnawing, and increasing in intensity. The pain at first is from pressure on the nerves by the infiltration; later, after ulceration occurs, the nerve terminals are exposed. As the growth usually extends to the anterior vaginal wall or in the cellular tissue between the uterus and bladder, vesical symptoms become more prominent—at first frequent desire to urinate, later intense vesical tenesmus, and finally perhaps perforation with formation of a fistula. As the growth increases the ureters become embedded in the cancerous mass, not pushed aside as in benign growths. The calibre of the ureters becomes constricted, either by compression without or by the involvement of the walls, producing hydronephrosis or pyonephrosis, and later on symptoms of uræmia. This last symptom is rather a source of comfort to the patient, as it blunts her intelligence and sensibilities.

The rectum is not so frequently affected as the bladder, but its involvement occurs in about twenty-two per cent. of the cases. Constipation usually is present, though this sometimes alternates with diarrhœa. There is generally some tension of the abdominal walls, more marked after the peritoneum is involved. As a rule the inguinal glands on one or both sides are enlarged, and œdema of one or both limbs appears from compression of the larger veins in the pelvis. The disease rarely attacks the bones of the pelvis.

Among the general symptoms one of the earliest is anorexia, nearly always present and lasting throughout the course of the disease. Vomiting or nausea may occur early, but these are usually not constant symptoms, as they are in the more advanced stages. After ulceration, and when the disease has extended to the surrounding structures, there is often a slight elevation of temperature at night, to 100° F. or a little higher, and is due to either a parametritis or to sapræmia. The absence of sepsis or pyrexia in cancer is due to the infiltration beneath the ulcerating cavity preventing the entrance of infective germs and septic absorption. These conditions, added to the hemorrhages and wasting discharges, the pain, and loss of sleep, are soon followed by emaciation and loss of strength. Prior to or about this time the condition known as cancerous cachexia is established. This is due to the malignant toxæmia, and in part to the exhaustion produced by the loss of blood and serum in the prolonged discharges. The expression is one of despondency, weariness, and constant physical suffering. The skin at first has a grayish hue, later a yellowish or icteroid pallor. It is harsh and dry. The last stages of the disease present no new or important symptoms, but only an exaggeration of those mentioned and an increase of suffering, unless an acute or chronic uræmia supervenes. Death in the majority of cases is due to exhaustion from lack of nutrition, depletion by hemorrhages, and the exhaustive discharge. Uræmia claims a large death rate, according to some authorities as high as forty-five per cent., though uræmic convulsions are rare. Peritonitis is another frequent cause of death. Other conditions, as hemorrhage, pyelonephritis, embolism of the pulmonary artery, pneumonitis, and metastasis to other organs—which, however, is not common—may be enumerated as causes of death.

DIAGNOSIS.

As a rule the diagnosis is easily made, because the disease is well advanced when it comes under observation. The sensation imparted to the finger when an examination is made is that of an excavated area covered by a brittle mass that feels like sand. The surface bleeds easily when touched, and is surrounded by ragged, indurated edges. There is more or less fixation of the uterus, and the examination with the finger is usually sufficient to warrant the diagnosis of cancer of the cervix. This is the stage and condition most frequently seen, but for a diagnosis to be of value it must be made early, and will vary with the variety and stage of the disease.

The *papillomatous* variety is the one most easy to recognize. It may commence as a dark-red or livid spot on the cervix, which bleeds easily when touched. As the disease progresses there will be seen, springing from the cervix, either an irregular, granular protuberance or a cauliflower-like mass, filling more or less the vagina, and covered with a non-odorous mucopus. The mass is exceedingly friable, and bleeds easily when touched. The base will be found broad and somewhat indurated. There is no pain on pressure nor is the uterus fixed. It may be mistaken at this period for an indurated cervix with erosive and cystic degeneration. In this latter condition we find the cervix more smooth and elastic, nor has it the defined indurated base or friable characteristics of the cancer.

Later on, after ulceration has commenced with some destruction and infiltration of the tissue, cancer may be confounded with an everted lacerated cervix with cystic and papillary hyperplasia. The diagnosis is sometimes difficult in the extreme, and that this condition is a prominent predisposing cause of cancer all gynecologists agree. The presence of numerous follicles on the cervix and margins, the fissure corresponding to the laceration on approximating the edges, and the absence of friability in the tissue, all point to the benign character of the disease. Cancer is usually limited to one wall, has a duller red mottled appearance, interspersed with yellowish-gray areas. The characteristic discharge and the result of treatment are all of diagnostic value.

A sloughing fibroid polypus, extending through the cervix, is excluded by the fact that it is surrounded by the thin dilated cervix. All sessile papillomata or villous growths of the cervix should as a rule be looked upon as malignant.

The *nodular* or infiltrated form is more difficult of diagnosis. There may be one or more nodules present, either external or internal to the os. If situated in the canal, the differentiation between carcinoma and myoma is quite difficult. The myoma is felt to be less intimately connected with the surrounding tissue, which is normal. In carcinoma the nodule is surrounded by infiltrated hardened tissue. The mucous membrane is not adherent to the myoma as it is in cancer, nor is the tissue of the myomatous growth friable.

A chancroid of the cervix may be recognized by the sharp thin edges of the ulceration, by the absence of the induration, and by the yellowish surface covered with pus of less offensive odor; a chancre by the constitutional symptoms that quickly follow, and by the result of antisyphilitic treatment.

Before ulceration is well established cancer of the cervical canal may present only the symptoms of a cervical endometritis. It commences as an infiltration in the cervical mucous membrane or just below it. Ulceration occurs earlier in this form than in the nodular, but up to that period the symptoms and appearance do not differ from those of a long-standing cervical catarrh. If the seat of the disease is in the upper part of the cervix, it may be shelled out by the destruction of tissue and the cervix has still the appearance of being normal. Such is not the case when the disease is at or near the external os. The introduction of a sound will reveal the excavated condition, as does also the offensiveness of the discharge point to malignancy. A test of diagnosis on which great reliance is to be placed in all carcinomatous growths is the friability or brittleness of the tissue. This is well demonstrated in using the curette. The cervix having been exposed, an attempt is made to scoop out some of the diseased tissue. If it be malignant, the curette will cut through deeply and a definite piece will be removed. The tissue will be found to be soft and cut like marrow until the infiltrated and inflamed base is reached. Such is not the case with inflammatory deposits or benign growths. The surface will bleed and only a few shreds of tissue will be removed. In all cases, especially if there is doubt, the diagnosis should be confirmed by the aid of the microscope. Care must be taken that the tissue for examination should not be removed too superficially, but should include healthy as well as diseased structure. The value of microscopical examination is questioned by many clinicians of repute, and in some instances the results may be negative, but in many cases it will give positive evidence of the character of the tissue examined.

Cancer of the Body of the Uterus.

Primary carcinoma of the body of the uterus as compared to that of the cervix is rare, and by older writers was thought to be extremely rare; but, thanks to methods of modern investigation, we know it to be far more frequent than was formerly supposed. In a vast majority of the cases it is secondary to cancer of the cervix, ovaries, or other adjacent organs. In a paper on the subject Beyea states that the statistics of all authors show that primary cancer of the body occurs most frequently between the ages of fifty and sixty, and that it is most often found in nulliparous women.

PATHOLOGICAL ANATOMY.

Primary carcinoma of the body may be either papillary or nodular, usually the former. Whether or not the nodular or deep-seated variety is primary in the body is uncertain. Klebs holds that both forms originate in the vicinity of the internal os from the Nabothian glands. Ruge and Veit maintain that they develop from the endometrium.

The *villous or papillary form* may be diffuse or circumscribed. In the diffuse variety the entire endometrium, from a point just above the internal os, is covered with a soft, friable mass, filling the cavity and bleeding readily, and considerable subendometrial infiltration may be present. In rarer instances single polypoid growths are observed, smooth in outline, filled with a dark pulpy mass of fungoid vegetations, attached to the endometrium by a broad or narrow pedicle.

The papillary form, together with an infiltrated base, may be localized, and if rapidly growing induce by its pressure atrophy of the opposite wall; if of slow growth, hypertrophy of the entire uterus takes place, due to the accompanying irritation (Ruge and Veit).

In the *nodular form* the growth is usually diffuse and spreads towards the peritoneum rather than towards the endometrium. Ulceration of the mucous membrane is uncommon. Section of a carcinomatous uterus shows the cancerous tissue as light, shiny bands, extending outwards towards the muscular tissue. As the growth enlarges it gradually obliterates the areas of normal tissue included by these bands, and appears as a uniform mass.

Extension from the endometrium to the cervical mucous membrane very seldom occurs, and then only late in the disease, when the extension is general.

Microscopically the glandular type is usually found, coinciding with Ruge and Veit's theory that carcinoma of the body always originates in the glands of the endometrium. They have described two forms. In the first the multiplication of the epithelial cells takes place superficially, and there is a tendency to spread laterally and into the uterine cavity. This proliferation may be general throughout the gland, or may occur at one point in the acini or duct of the gland, where a heaping up of the cylindrical cells will entirely occlude the lumen. In the second form the glands send shoots down into the underlying connective and muscular tissue, while between and beyond these processes will be seen the groups or nests of cancer cells. More stroma is always observed in this form. The great quantity of cylindrical epithelium distinguishes this variety from the ordinary lobulated pavement epitheliomata of other parts.

SYMPTOMS.

The most constant symptom is hemorrhage occurring after the menopause. It is at first slight, and usually the only symptom present. The bleeding often continues a long time before the patient seeks treatment. There may be slight pains and other reflex symptoms in the commencement of the growth, similar to those of a chronic endometritis. The next prominent symptom is the discharge. It is thinner, not sanguineous, and, though fetid, much less offensive than that of cancer of the cervix. This latter condition may be due to the absence of bacterial infection, which occurs later in this form on account of the location of the disease. It is partly due to the same reason that the sapræmic symptoms do not occur so early as in cancer of the cervix. Pain, as has been stated, is at first slight, but as the disease progresses assumes a paroxysmal character, and is almost pathognomonic of cancer of the body when present, though occasionally it does not accompany the disease. It may recur at certain hours of the day and resemble in character that of uterine colic. It has been attributed by Schroeder to contraction of the uterus trying to expel the growth, but Pozzi claims it is due to a neuritis incident to the ulceration and not to uterine contractions. These prominent symptoms all become aggravated with the duration of the disease; the hemorrhage is more profuse, the discharge is dark, dirty, grumous, and much more offensive. The pain and suffering increase, especially after peritoneal involvement, but as a rule are not so great as in the cervical form. Then cancerous cachexia, anæmia, and emaciation soon follow. The other symptoms arising from cancer of the uterus are late in appearing. Metastases are often absent. Invasion of the lymphatics and surrounding tissue does not occur early; even in the later stages we sometimes find the uterus movable.

Bimanual examination finds the uterus enlarged, but in the early stages this is not recognizable. The cervix is soft and patulous, as in the gravid uterus—perhaps sufficiently so to admit the examining finger and allow the growth to be felt. The introduction of a sound is followed by hemorrhage, but shows an increased capacity and gives the impression of roughness, of irregularity, of a friable mass in the cavity of the uterus. This later symptom of brittleness is significant of malignancy.

DIAGNOSIS.

The diagnosis is made clinically from the symptoms already described and with the aid of the microscope. In curetting the uterus to secure the specimen for examination, the curette should be applied to every portion of the uterine canal, as the disease may be limited to a small portion and the shreds of tissue removed may not indicate malignancy though it be present. The diagnosis in the early stage may be difficult, particularly if the hemorrhage and discharge are late in appearing.

The return of irregular hemorrhage after menstruation has ceased perhaps for years, or the return of a leucorrhœal discharge in one unaccustomed to it should arouse the suspicion of cancer if there is found no disease of the cervix or if endometritis is present. In case of a sloughing myofibroma before the menopause, the symptoms may make the diagnosis doubtful until a microscopical examination is made, but this condition is very rare. The hemorrhage, in case of a myofibroma, is profuse and the discharge is watery and not offensive. Dilatation of the cervix and intrauterine exploration will aid in removing the doubt. Retained products of conception will sometimes produce symptoms indicative of malignant growths, but these can be dissipated by the history of the case and the use of the curette. Fetid endometritis in old women, which occasionally occurs, will make a diagnosis very difficult. We have to rely here chiefly on the persistence of the symptoms after curetting and the microscopical examination of the specimen removed. If in any case a positive opinion cannot be given from one microscopical examination, the course of the disease should be closely watched and subsequent microscopical examinations should be made.

PROGNOSIS.

The prognosis is very unfavorable, the average duration being about two years. According to some writers it is slightly more favorable than that of malignant disease of other portions of the organ. It is some time after the initial symptoms are present before lymphatic infection occurs, and this offers a better chance of complete removal.

Sarcoma.

Sarcomata of the uterus have but recently been differentiated from other uterine neoplasms. Many doubtful cases described by writers fifty years ago now are plainly seen to be sarcomata. Uterine sarcoma occurs at an earlier age than cancer—Zweifel having reported a case in which he performed a hysterectomy on a patient, thirteen years of age, for sarcoma of the uterus; yet, according to Gusserow, twenty-eight cases in a series of seventy-three occurred between the ages of forty and forty-nine, showing that the predisposition which exists during the menopause to cancer also pertains to sarcoma.

Unlike cancer, sarcomata occur with greater frequency in sterile women; in sixty-three cases reported, twenty-three had never borne children.

Pathological Anatomy.

Sarcoma of the cervix is very rare. The cases described have been of the polypoid form, the majority of them being those known as "grape-like" sarcoma. They are composed of many lobules, are of a cyanoid appearance, and consist of sarcoma cells and some fibrous and muscular tissue. Sarcoma of the body originates either in the endometrium or the parenchyma, the first occurring most frequently. J. W. Williams, who has written exhaustively on the subject of uterine sarcoma, says: "The interstitial and submucous sarcomata have a marked tendency to make their way towards the uterine cavity and there assume a polypoid form, so that it is frequently impossible to decide whether a given polypoid sarcoma arises primarily from the parenchyma or mucosa." Two forms are described, the circumscribed or polypoid, and the diffuse or infiltrating. Sarcomata of the endometrium are usually located some distance above the cervix, frequently in the fundus. The circumscribed sarcoma varies from a small nodule in the mucous membrane to a polypoid growth which may extend into and beyond the cervical canal. The diffuse sarcomata occur as a uniform thickening of the mucous membrane, which appears rough, at times gangrenous, and is often covered with ragged villi. They are remarkably vascular and bleed very readily and freely.

In sarcoma of the parenchyma the most frequent form is the circumscribed. While they are not encapsulated, yet their fairly distinct limitations cause them at times to be mistaken for a myoma or fibroma. Diffuse intramural sarcoma is of so rare occurrence that its existence is ignored by many writers. The growth develops in and spreads along the connective tissue surrounding the muscular fibres, soon extending to the endometrium and the subperitoneal connective tissue. Microscopically the sarcomata consist of round, spindle, or giant cells embedded in a peculiar fibrillar tissue. Often the cells so greatly predominate as to obscure the scant amount of basement membrane present, but there exists an intimate relation between each cell and this fibrous framework. According as one or another form of cells predominates, the tumor is known as a round, spindle, or giant cell sarcoma; yet a combination of any two or all three may occur. These tumors spring from the connective tissue or stroma of the part, sometimes originating in the walls of the blood-vessels. The blood supply is usually very abundant, and the vessel walls become infiltrated or replaced by the tumor cells. This free communication between the blood current and the constituent elements of the tumor accounts for the occurrence of metastases through the blood-vessels. Metastatic deposits are of comparatively rare occurrence in sarcoma, and when they do occur it is at distant points of the body—a fact explained by the peculiarities in the blood supply. In this connection it may be noted that one of the important points which serves to distinguish between deciduoma malignum and sarcoma is that in the former extension to the vaginal and other neighboring parts is common and early. The round-cell sarcomata grow with greatest rapidity and are the most malignant, while the spindle-cell variety are of slower growth and less malignant. The greater the number of cells, the more likely is the tumor to recur and the greater is its tendency to develop metastases, because of the lack of intercellular substance to maintain the integrity of the part. Hence the generally recognized opinion that soft tumors are most malignant. Fibrosarcoma is simply a form of sarcoma in which the intercellular tissue is present in large quantities.

The statement that fibromyomata undergo sarcomatous degeneration has been disputed, yet there is little reason to doubt it. J. W. Williams lays stress upon the lack of microscopical evidence of the degeneration of fibromatous tissue into sarcomata. He shows that while von Kahlden, Heger, Leopold, Kunert, Schroeder, and others all maintain that such a change does occur, upon close scrutiny their illustrative cases do not fully support their assertions. Too often the diagnosis of such a change has been made on clinical or macroscopical findings, while the decisive microscopical examination has been omitted. With regard to the sarcomatous degeneration of the myomatous tissue of fibromyomata, Williams has exhaustively described a case which is apparently conclusive. He demonstrates the transition of muscle cells into sarcoma cells, denominating the growth "myoma sarcomatodes."

This possibility is of great importance clinically. In cases of fibromyomata recurring after removal, the possibility of malignant transformation should be borne in mind.

Adenosarcomata have been reported. In many of the so-called "grape-like" sarcomata the presence of glandular tissue has been described, but these cases are not free from the inference that this tissue is but the remains of normal glands included in the sarcomatous growth. The same explanation may be applied to sarcomata of the body, in which glandular structure is recognized.

SYMPTOMS.

The symptoms of the two forms differ. In the diffuse variety they clearly resemble those of carcinoma—hemorrhage, at first intermittent, then almost continuous; serous discharge becoming sanious, and after ulceration, fetid; and enlargement of the uterus. There is no distinct tumor to be felt, but there is a general enlargement of the uterus, and the growth may be seen presenting itself through the os uteri. Pain is variable, but often most severe. It is not, according to some writers, due to the expulsive efforts of the uterus, to which it has been credited, as much as to "some morbid changes in the terminal nerve filaments." Its severity depends somewhat on the depth the sarcomatous infiltration has penetrated. It is of a boring, lancinating character. In the later stages the hemorrhage is more profuse, the discharge more offensive and contains sloughs or shreds of tissue, and if in addition to these symptoms we find loss of strength, anæmia, and cachexia, the diagnosis is easily made. On physical examination the cervix is patulous. The finger will detect in the cavity of the uterus a spongy mass, friable, bleeding easily, springing from a portion of the wall of the uterus.

Fibrosarcoma.—At first there is no difference between the symptoms of a fibromyoma and those of a fibrosarcoma. In both there is the hemorrhage producing either menorrhagia or metrorrhagia, and a watery non-offensive discharge. Some pain is usually present, the amount depending on the uterine contractions excited by the presence of the tumor. The fact that a fibromyoma, which is known to exist in a patient and which should diminish after the climacteric or give no trouble, suddenly begins to grow and produce symptoms will awaken suspicion that the tumor is undergoing sarcomatous degeneration. Later on ulceration occurs; the bleeding becomes continuous and more excessive; the discharge more profuse, sanious, then fetid, containing shreds of broken-down tissue. The pain resembles labor pain, is paroxysmal in character, and increases in severity. The uterus is much increased in size and may be displaced. The cervical canal is dilated and patulous, and the tumor may present itself at the os or may be expelled into the vagina. The finger will detect a friable, bleeding tumor, from which pieces can be removed with little pressure. Sometimes the mucous membrane may be found smooth, but at one point there will be found a tumor in the wall, which has become ulcerated and from which the discharge comes; or again, very rarely numerous sarcomatous nodules may be felt. The cachexia becomes progressive with the disease, and death from marasmus, peritonitis, sepsis, ileus, or uræmia ensues. Metastasis is more common in this form than in the diffuse variety.

DIAGNOSIS.

The diagnosis of sarcoma of the uterus can be positively made only by the use of the microscope. Pieces of the tissue for examination should be removed deeply with the curette. The rapid growth of a long-standing fibromyoma at or about the menopause, with rapid anæmia and deterioration of health, is indicative of malignancy. When the growth is soft, friable, and can be readily penetrated by the examining finger, the diagnosis can be made, with one exception—that is, of a sloughing fibroid. In this latter condition a microscopical examination would be of valuable assistance in solving the doubt. In the diffuse sarcoma the diagnosis is very difficult. We have to rely almost entirely on the microscope, along with the clinical history. The differentiation between this form and diffuse adenoma of the uterine walls in the early stage is extremely difficult. The latter generally occurs before the menopause; the uterus is not enlarged, the growths are superficial, never involving the deeper uterine structures, nor is there the rapid deterioration of health.

PROGNOSIS.

This is usually unfavorable, unless the disease is discovered sufficiently early to permit complete removal. The disease recurs most quickly in young patients, and is said to have a more rapid course in them. Compared with cancer the prognosis after hysterectomy is better, as its extension and lymphatic invasion are slower. The duration of the disease is from four months to six years, the average being about two years.

Malignant Adenoma.

Malignant adenoma has usually been considered a distinct form of tumor, but upon closer study of the clinical and microscopical evidences it is plain that this growth is but an early stage of glandular cancer.

To differentiate between a benign and malignant adenoma is not easy. The benign form consists microscopically of newly formed alveoli lined by a single layer of cylindrical cells. The malignant variety shows these cells greatly increased, ultimately producing solid tubes of epithelial cells. "In malignant adenoma the proliferation of the gland cells is atypical; furnished with a single layer of cylindrical epithelial cells, they are folded upon themselves and rolled up into glomeruli; the fibrous substratum has almost disappeared and the glands touch each other at many points; and there is no boundary between the glands and the uterine tissue" (Pozzi). A truer description of beginning cancer could hardly be written.

That benign adenoma or so-called glandular endometritis may degenerate into a malignant adenoma or cancer undoubtedly is true, but it does not follow that all glandular cancers are preceded by a stage of benign glandular increase.

Deciduoma Malignum.

The most malignant of uterine neoplasms is the so-called deciduoma malignum. It has been described under various names as syncytial carcinoma, sarcoma deciduocellulare, chorioepithelioma, serotinal tumor, and the one suggested by Sänger and most commonly used, deciduoma malignum. These various names indicate the uncertainty entertained as to its proper pathological position. While some writers incline to the opinion that it is a modified cancer or sarcoma, yet the majority consider it a distinct form of neoplasm. As will be further seen it is essentially an epithelial growth, of which the characteristic structure is a large, irregularly shaped polynuclear cell. The resemblance to sarcoma consists in the cellular tissue surrounding these masses.

ETIOLOGY.

Very little is known of the cause of this neoplasm. Apparently nothing in the family history or the previous condition of health bears any relation to it. It has never been known to occur except during pregnancy or immediately following abortion or childbirth. It occurs in comparatively young women, the average age in twenty-six cases being 23.7 years. According to Williams in forty-five per cent. of the cases collected by him the disease developed subsequent to hydatidiform mole, a fact strongly suggestive of some etiological relation between these two affections.

PATHOLOGICAL ANATOMY.

The growth originates in the placenta, or at its site. It is usually somewhat circumscribed and embedded in the uterine wall, a fact which aids in differentiating it from retained placenta, or débris, or blood clots, but it may become diffuse and rapidly involve the fundus, in some instances extending down to the os internum. The growth is dark in color, contains many blood clots, some partly organized, and is of soft consistence, having a pulpy feeling like placental tissue, and somewhat resembling a villous cancer of the endometrium. Ulceration and necrosis ensue early, giving rise to frequent alarming hemorrhages and a profuse fetid discharge. The growth extends into the muscular tissue, and the uterine wall becomes soft and easily perforated.

Microscopically the growth consists of a great variety of cells. Round, epithelial, and giant cells are all found upon examination. The characteristic giant cell is composed of a mass of homogeneous protoplasm, apparently without any limiting cell wall, containing from two to fifteen, or even more, irregularly shaped nuclei. Williams believes these giant cells to be simply cross sections of masses of syncytial protoplasm containing free nuclei. The other cells are red and white corpuscles, round and spindle connective-tissue cells, and mononuclear decidual cells, all lying in a meshwork of fibrin. The last-mentioned cells constitute a factor in the development of the tumor, but for the purpose of microscopical diagnosis the giant cell must be found. These tumors are very vascular, the blood being found in irregular spaces or channels, while blood-vessels are wanting in the intervening tissues. The tumor cells compose the walls of these spaces, and metastases by the blood-vessels occur because of this peculiarity of structure. The frequent and copious hemorrhages are due to extension of the ulcerative process through the walls of these blood spaces.

There seems to be no doubt that the point of origin of these tumors is in the epithelial cells covering the chorionic villi. In this connection Marchand, in a comprehensive review of the subject, gives his conclusions, some of which have met with general acceptance, and may be quoted: (1) "The formation of metastases occurs almost invariably by way of the blood-vessels; (2) the connective tissue of the chorion is not known to participate in the development of the tumor; (3) all the tumors are epithelial, the tissues combining in their formation being (*a*) the syncytium, *i.e.*, the uterine epithelial layer of the chorion; (*b*) the elements of the so-called cellular layer

(layer of Langhans), *i.e.*, the ectodermal epithelium of the chorion (these two orders of elements form a normal constituent of the serotina); (4) hydatid-mole pregnancy favors the occurrence of malignant neoplasms, inasmuch as the epithelial elements penetrate the serotina more deeply than in normal pregnancy; (5) the decidual cells, properly so-called, do not participate in the formation of the malignant neoplasms, or only in a very small degree at the primary site of origin; (6) the elements of the cellular layer (of the ectoderm) most frequently occur as polyhedral clear cells containing glycogen, they multiply by direct division of the nuclei, they vary in size, but are usually smaller than those of the syncytium."

Extension.

Rapidly fatal as the disease is, in two-thirds of the cases extension to the cervix, vagina, broad ligaments, and other adjacent tissue occurs, or distant metastases are found in the lungs, kidneys, liver, stomach, spleen, brain, and intestines or other organs. J. Whitridge Williams reports a case of metastasis to the vulva within two weeks after delivery.

In suspicious cases it should be borne in mind that repeated curettage to relieve the symptoms hastens the occurrence of metastases.

SYMPTOMS.

Hemorrhage, following abortion or labor, is the first symptom. While at first intermittent and scanty it soon becomes more profuse, despite such measures for relief as curetting or tamponment. Cases are reported in which hemorrhage was absent until after the appearance of metastases, but this is extremely rare. The hemorrhage is followed by a brownish, watery discharge, containing masses of the growth, and of a decidedly offensive character. The characteristic cachexia of malignancy and anorexia and anæmia, dependent upon the amount of hemorrhage, soon appear with elevation of temperature and marked emaciation. Upon examination the os is found to be soft and usually open, and the uterus is enlarged, soft, and spongy. It will be observed upon passing the finger into the uterine cavity that the uterine wall is extremely friable, the finger sinking deep into the muscular tissue upon the slightest pressure, and portions of the growth may be thus removed. Further examination will reveal metastatic nodules in the vagina, broad ligaments, tubes, and ovaries.

DIAGNOSIS.

Usually the clinical signs are sufficient to make the diagnosis. Although the disease is rare it should always be suspected in cases of hemorrhage following the apparently complete expulsion of an hydatid mole.

The hemorrhage and later the sanguineous fetid discharge, together with the history of recent pregnancy, are all grounds for suspecting malignant disease, and the uterine contents should be microscopically examined. Sinclair concludes: "When the uterus has been explored and the curette used once for all, if there be a recurrence of hemorrhage and foul discharge, there is also a recurrence of a malignant neoplasm."

PROGNOSIS.

If left to itself the disease rapidly and invariably proves fatal, death usually occurring in from three to six months from exhaustion. Some cases are reported as lasting as long as ten months, but they are of infrequent occurrence. For a malignant disease the prognosis appears to be singularly favorable, provided proper surgical treatment be instituted early enough.

Treatment of Malignant Diseases of the Uterus.

The treatment varies with the conditions that are found—radical when the neoplasm is limited to the uterus and can be entirely removed, and palliative when the disease has passed beyond the uterus and invaded the surrounding structures, which makes complete removal impossible. In this condition the indications are to relieve the many complications that have been seen to follow the course of this disease.

PALLIATIVE TREATMENT.

This should be directed to the prolongation of life and the relief of suffering.

The *general treatment* consists in building up and sustaining the system by suitable food in sufficient quantity to insure the regeneration of tissue and strength. Animal foods largely tend to this effect. Alcohol, which retards waste-tissue elimination, is contraindicated, and according to some writers has a predisposing influence in the production of cancer. The bowels should be kept regular, but not too free. The kidneys should be watched and the renal secretion stimulated by diuretics if indications arise. The liver should be made to do its part in the elimination of effete material, and the skin to perform its functions by hot baths with friction afterwards, or by frequent baths and massage.

The use of medicinal agents for the control or cure of cancer has been uniformly unsuccessful in the hands of careful observers. Various remedies have been brought before the profession as specifics, but they have been weighed in the balance and found wanting. At one time Chian turpentine, recommended by Clay, of Manchester, and indorsed by others, was a popular remedy in the treatment of cancer, but has been found to be devoid of any effect, except upsetting the patient's digestion. The condurango craze had an extensive run about twenty years ago, but the drug was found to be of little value except in stimulating the appetite and digestion. Then chalk, used as first prepared from calcined oyster shells, given in doses of twenty grains three times a day, was largely employed. Arsenic has for a long time been used in cancerous cases. It is an alterative and good tonic, but that it exerts any specific curative effect on the growth we do not believe. Lately pyoktanin or methyl blue has been claimed to be of value, but we have failed to see any beneficent effect from its internal use. It is given in doses of three or four grains, once or twice a day. Sometimes it is necessary to do something on account of its moral effect for these unfortunate patients. Then these remedies may be used, more for that purpose than with the expectation of any beneficent results. It is better to resort to some drugs that will improve the appetite and digestion, or stimulate the excretory or secretory functions. A combination that I frequently employ is one of bichloride of mercury and Fowler's solution of arsenic, with tincture of cinchona bark as a medium. Opium should always be used for the relief of pain, which is usually such a prominent symptom. It should be increased in quantity as the necessity for it arises. A woman who has only a limited period to live has a right to expect her life to be made as comfortable as possible, and it is the essence of cruelty to withhold opium from any moral or ethical ideas. Opium does not hasten the end, but prolongs life by the rest it secures to the patient.

We should never inform the patient of the nature of her disease unless she persistently demands it, for it is cruel to deprive a woman of all hope of recovery from a disease that may last several years.

Local Treatment.—In inoperable cases, local treatment, which to some extent is surgical, is of great value for the relief of suffering and the prolongation of life. Hemorrhage and the excessively fetid discharge are two complications which largely aid in the deterioration of health and in the production of discomfort and suffering. The best means to control them is by the sharp curette, and the best instrument for this purpose is the spoon curette of Simon. Care should be taken not to perforate the vaginal walls into the bladder or rectum, which is easily done when the walls are infiltrated. As much of the diseased tissue should be removed as possible, and the action of the curette supplemented by an escharotic or the cautery. Chloride of zinc is a valuable caustic in the treatment of cancer of the cervix. It should be applied in the following manner: After as much of the growth has been removed as possible, the bleeding is to be checked by pressure, packing with gauze the bleeding surface or cavity, or by using gauze saturated in a five-per-cent. solution of antipyrin. This is usually sufficient to control the hemorrhage, but if not so the packing should remain twenty-four hours, when the application of the chloride of zinc is made. It is applied by soaking pledgets of absorbent cotton in a fifty-per-cent. solution, the excess of fluid being squeezed out, and the pledgets applied to the surface or cavity. It should be retained in place by tamponing the vagina with gauze saturated in a bicarbonate of sodium solution to protect the vaginal walls by neutralizing the effect of any of the caustic which might escape. This protection may also be made by smearing the vaginal walls with an ointment of bicarbonate of sodium and vaseline. The application should be removed in forty-eight hours and vaginal antiseptic douches given. The slough caused by this treatment is deep and follows up the diseased tissue. It is usually separated in from eight to ten days. The operation is not usually painful, and if done rapidly local anæsthetics may be used. Great care should be exercised in protecting the vulva and vagina from the caustic, as its contact there would entail useless suffering. Various other caustics have been used, as nitric acid, chromic acid, and five-per-cent. alcoholic solution of bromine; but none is so valuable as the chloride of zinc. The proximity of the peritoneum, bladder, and rectum should be remembered in using the curette or caustics, as severe hemorrhage and perforation have followed their employment.

The cautery is one of the best methods of dealing with inoperable cases of cancer of the uterus. It is a great favorite with the Germans. The galvanic is the best, as the heat can be more easily controlled. The Paquelin cautery is a very valuable instrument, and is largely used in this country. The vaginal walls should be protected against the effect of the heat; a narrow shoe horn is useful for this purpose, and an occasional injection of a cold antiseptic solution will keep the temperature down. The cautery should be kept at a dull-red heat, as that temperature controls the hemorrhage. The surface should be burnt deeply and until all oozing has ceased, and then the cavity is to be packed with gauze. It is preferable to remove as much of the tissue with the curette as possible before applying the cautery. While the slough or shreds of tissue are being separated, disinfectant douches four or five times a day should be used. All the cases in which I have used this treatment have been followed by general improvement as well as amelioration of the local symptoms.

Hypodermic injections of chemical substances just beneath the infiltrated parts have been tried—bichloride of mercury, salicylic-acid solutions, and more recently alcohol. Schultz, of Budapest, reports a series of thirty cases treated with alcohol in this manner, and claims that the result was satisfactory, but it is very painful to the patient.

The application of protonuclein to the ulcerated surface has been made, and some success has been reported. I used it in one case after curetting, with marked local improvement, but was not able to follow up the case. Carbide of calcium locally has lately been recommended by Etheridge, of Chicago, who reports gratifying results.

As the disease advances, the objects to combat are the hemorrhage and the foul discharge. One saps the patient's strength and produces anæmia; the other poisons her and makes her an object of distress and disgust to herself and those around her. The hemorrhage may be arrested by pressure with a tampon placed against the bleeding surface; some astringent, as tannin or alum, may be used, or a five-per-cent. solution of antipyrin is valuable. The styptic effect of the salts of iron may be tried if these other agents fail. The foul discharge should be combated by frequent disinfectant douches. Creolin is one of the best; carbolic acid is useful, and permanganate of potassium, enough to give the water a dark-purple color (ten grains to the ounce), may render good service. Peroxide of hydrogen has no odor and has a high disinfectant power.

Sometimes an alkaline solution is soothing, and copious injections of salt and water are useful. The application of iodoform and charcoal, of iodoform and tannin, of aristol, and suppositories of chloral and tannin are very useful in combating hemorrhage, pain, and odor. The discharge frequently produces vulvitis and a dermatitis of the thighs and groin. This may be controlled by great personal cleanliness, by bathing with lead water, and greasing the parts with borated vaseline.

RADICAL TREATMENT.

The only treatment for cancer of the uterus that holds out a prospect of a cure is the thorough removal of the disease. We think it the duty of the practitioner, not only to realize this fact himself, but to impress upon his patients the importance of an early diagnosis of cancer of the uterus and the necessity of consulting a competent physician when peculiar or unaccustomed uterine symptoms manifest themselves. Especially is this so in the case of women about the menopause, when irregular, bloody, or serous discharges are supposed to be natural. Again, patients having cervical laceration should be watched after thirty years of age, and in case of family predisposition to cancer the laceration should be repaired, even though the pathological condition of the cervix is slight. I believe that in all cases of laceration when the cervical lips are thickened and infiltrated, associated with cervical endometritis, depletion and repair should be practised. Should this method be generally adopted, a great many cases of cancer of the uterus would be avoided or would be seen in the incipiency of the disease, and failure to cure by hysterectomy would be rare compared to what the results are now. When careful examination shows that the disease is not limited to the cervix or uterus, but has involved the parauterine tissues (vagina, broad ligaments, pelvic cellular tissue, bladder, or rectum), so that complete removal is impossible, hysterectomy is contraindicated; and the interest of the patient is best subserved by palliative measures.

The radical treatment of cancer of the cervix is either amputation of the cervix or hysterectomy. The latter, in my opinion, is always to be preferred, because it is unquestionably the more thorough, and because we can never tell when the disease has extended to the body. A comparison of the immediate and remote results of the two methods is interesting, and we are impressed with the favorable statistics furnished by the advocates of the different methods. I do not believe these statistics would be so close if the comparison was made of cases of similar pathological conditions. Evidently supravaginal amputation of the cervix would be justifiable only when the disease is limited to the cervix; therefore it is necessarily done at an earlier period than that at which hysterectomies are frequently performed—which is often, indeed, when the cervix is completely destroyed by the growth, and there is much greater risk of lymphatic involvement. The only way to test the comparative value of the two operations would be to take a number of cases of like pathological conditions and subject them to the test.

Among the prominent advocates of amputation of the cervix are Schroeder, Winter, Verneuil, Skene, and Byrne. The remote results they publish of this method of treatment are remarkable. Winter claims a death rate of 6.5 per cent. from the operation; 38 per cent. remained cured after two years, and 26.5 per cent. after five years. J. Byrne, of Brooklyn, recently published the results of 81 cases treated by removal with the galvanocautery. There had been no recurrence after seventeen years in 1 case, after thirteen years in another, eleven years in 2, seven years in 6, five years in 8, four years in 6, and after three years in 11 cases. In contrast to these statistics, Martin's experience should be quoted: Out of twenty-eight cases treated by supravaginal amputation, only two remained without recurrence.

The method of high amputation by excision was introduced by Schroeder in 1878. The technique as followed by him is briefly as follows: The vagina and cervix are cleansed by scrubbing with soap, followed by antiseptic douches. The cervix is grasped with a pair of strong volsellum forceps, and drawn down as far as possible; two ligatures are passed through and above each lateral cul-de-sac, to embrace the uterine artery, and tied. A transverse incision is made through the anterior cervicovaginal juncture as far as possible above the diseased part, and the bladder is separated with the finger or scalpel handle as high as the internal os. The forceps is then elevated to expose the posterior cul-de-sac, and a similar incision is made through the vaginal wall to the peritoneum. This is stripped off in a similar manner to the bladder, the two incisions are then joined, and the cervix is excised in a wedge-shaped piece with knife or scissors. The peritoneum is likely to be opened if great care is not observed, and if so it should be closed at once with catgut sutures. Sutures are then passed through the anterior and posterior vaginal walls on each side, embracing the parts deeply, coming out in the cervical canal. They should be tied so as to compress all bleeding and cover the stump with vaginal mucous membrane. Primary union may be secured by this method. The vagina is thoroughly cleansed and packed with iodoform gauze, which is removed in twenty-four or forty-eight hours, and daily antiseptic douches are given. The stitches, if not catgut, may be removed in ten days and the patient may be allowed to leave her bed.

High amputation of the cervix by the galvanocautery may also be performed. Byrne and Skene, of Brooklyn, still warmly advocate this method. The former has perfected the operation, and his remote results, which have already been referred to, are remarkable. After exposing the cervix with the perineal retractor the cervix is grasped and drawn down with a pair of volsellum forceps. By alternating traction upwards and downwards, the proper point to begin the circular incision may be obtained so as to avoid injury of the bladder, or opening the peritoneal cavity (in Douglas' cul-de-sac). Though, if the retrouterine tissues be involved, the operation should not be abandoned for fear of injury to the peritoneum, for the results of such an injury are said to be attended with little danger.

Byrne advises in the latter case to make the incision a little anterior to the diseased structure, and to let the removal of this part be the final procedure. A slightly curved cautery electrode knife is applied cold to the point of election, the circuit is then closed, and with a dull heat a circular incision is made round the cervix. After burning to the depth of a quarter of an inch, it will be seen that the uterus can be drawn farther down and by pushing the knife upwards the required depth may be obtained. In any case requiring amputation above the internal os the cervix should be removed first and a pair of diverging volsellum forceps introduced into the canal; the uterus is then pulled down and a higher amputation proceeded with in the same manner as before. The cup-shaped cavity should be tamponed with iodoform gauze, which is allowed to remain forty-eight hours. The after-treatment consists in the daily use of antiseptic douches. This operation may also be performed equally well with the curved knife of the Paquelin cautery.

Hysterectomy.

It is conceded by the vast majority of gynecologists that the treatment of sarcoma or carcinoma of the uterus, wherever situated, before infiltration of the adjoining tissue or lymphatic involvement has taken place, consists in complete and thorough removal of the organ, either through the vagina or by the abdominal incision. The operation of election, by the majority of operators, is by the vaginal method, because of its simplicity, the shorter time required for its performance, and the more comfortable and rapid convalescence, but, above all, for its lower mortality. Before operating, careful examination should be made to ascertain if the uterus is movable and that the parauterine tissues are not involved. For this purpose bimanual palpation and downward traction of the uterus with forceps are indispensable. Should the examination show the uterus fixed, or little movable, and bimanual palpation disclose swelling or induration (unless known to be inflammatory in origin) around the uterus, with invasion of the vaginal walls, the operation is contraindicated. The writer is aware in making this statement that it is opposed to the views and practice of many prominent operators, who often remove the uterus and portions of the adjacent diseased tissues with recovery of the patient from the operation, but his experience has been that under these conditions an early recurrence of the disease has invariably followed.

The operation of palliative hysterectomy should have no place in gynecology, for it is an abuse of scientific language, since it is an operation that frequently kills the patient and is far less palliative than curetting and cauterization. The immediate results of the operations reported in the last few years, in the hands of competent surgeons, are as good as we could desire. Its mortality varies from two to eight per cent. The latest statistics I have examined give a correct mortality of about five per cent. The remote results are not so good, but they are far better than those quoted ten years ago. The statistics of the best operators show freedom from disease two or more years after vaginal hysterectomy in about forty to sixty per cent. of all cases. The recurrence of cancer of the uterus after hysterectomy is less frequent than after its removal from other parts of the body; even in cancer of the breast, when the diagnosis is usually made earlier on account of its exposed position, recurrence more frequently follows operation, even when the subclavian and axillary glands have been removed. The modes of recurrence after operation are by metastases, by lymphatic recurrence, and by local recurrence. The latter is far the most frequent form, hence the importance of extending the incision as far as possible beyond the diseased tissues.

The space allotted will not permit a description of the number of, technically, more or less different methods of vaginal hysterectomy, that have been introduced and practised. The following method is the one I usually follow, and it is also practised by a large number of operators: Several days preceding the operation antiseptic douches are given; the morning of the operation the bowels are thoroughly moved; the bladder should be emptied at the beginning of the operation. The patient is placed in the dorsosacral position and the perineum is depressed by a speculum. The cervix is thoroughly curetted, then charred by a Paquelin cautery; a piece of gauze is introduced into the canal, and the lips of the os are sewed closely over it. The vagina is then cleansed again; lateral retractors being introduced, the cervix is grasped with a pair of volsellum forceps and dragged downwards. A free incision with scissors is made completely around the cervix, as far as possible from the disease. The loose vaginal tissues round the cervix are stripped back with the fingers or handle of the scalpel, keeping close to the uterus. This will allow the uterus to be drawn much farther down and lessen the danger of injury to the bladder and ureters. The bladder is then separated from the uterus by means of the fingers or closed blunt scissors until the uterovesical fold of the peritoneum is reached and opened. This opening is easily enlarged by introducing the two index fingers and tearing laterally to the region of the broad ligaments. The same method is adopted posteriorly until the peritoneum of Douglas' cul-de-sac is broken through and the opening enlarged. The hemorrhage from the vaginal incision is rarely sufficient to require special hæmostasis, but if preferred it can be controlled by catgut ligatures, as can also the peritoneum anteriorly and posteriorly be stitched to its respective vaginal edge. This, however, I rarely do, as the oozing ceases spontaneously when the uterine arteries are clamped.

When Douglas' cul-de-sac is opened, a large gauze sponge with a string attached (for the purpose of removal) is introduced to protect the pelvic viscera and absorb the blood. The index finger of the left hand is introduced for the purpose of drawing down the ligament and guiding a pair of strong forceps, with long jaws, which are made to grasp the uterine artery and a portion of the ligament close to the uterus. The same is repeated on the opposite side, when a single incision with the scissors severs the arteries and a portion of the ligaments they enclose. The uterus can now be drawn farther down, and is held only by the remaining portion of the broad ligaments. These in turn are clamped and the uterus is removed by a few strokes of the scissors. The application of the forceps to the broad ligament may be facilitated by *anteverting* or *retroverting* the uterus and drawing the fundus through either opening. Should the ovaries not be included with the broad ligaments they may be left, or secured by separate forceps. Sufficient tissue should be left on the distal side of the forceps to prevent slipping, for fatal hemorrhage has followed the want of this precaution. To prevent slipping of the locks of the forceps handles, they should be securely tied together. The completeness of the hæmostasis should be ascertained, when the gauze sponge is removed, and the forceps handles on each side are enveloped in a piece of gauze. A strip of iodoform gauze is then passed beyond the point of the last pair of forceps introduced, and Douglas' cul-de-sac is gently packed, the vagina tamponed with gauze, and the vulva closed with a pad held in place with a T-bandage. The after-treatment is simple. The forceps are removed in forty-eight hours. The vaginal tampon is left in place for four days. The strip which acts as a drain is removed in five or six days, when the peritoneal wound is well closed by exudation. The bowels are moved on the third day and vaginal douches are carefully given after the sixth day.

The operation of vaginal hysterectomy by ligature instead of the forceps is commonly known as Martin's method or some modification of it. It may be described briefly as follows: The cervix having been exposed is drawn sharply forwards and a transverse incision is made into the posterior cul-de-sac. The peritoneum is stitched to the vaginal membrane. The index finger of the left hand is introduced into the peritoneal cavity through the opening, and the vaginal wall on the left side is lifted up. A stout aneurysm needle or a strong curved needle threaded with a piece of silk is passed about a quarter of an inch from the border of the uterus and securely tied. This is repeated on the opposite side. The tissue included in the ligature, which also embraces the uterine artery, is now divided by scissors, and another ligature is applied in the same way a little higher up and the tissue is incised. The cervix is then carried backwards to stretch the anterior cul-de-sac and an incision is made transversely through the anterior vaginal wall, the bladder being separated with the fingers from the uterus until the anterior uterovesical fold of peritoneum is reached. This is opened and enlarged with the fingers. Nothing now remains but to ligate by successive stages the remaining portions of the broad ligaments. This part of the operation may be facilitated by grasping the fundus with a pair of forceps and bringing it down into either the anterior or posterior opening. The opening is partially closed and a tube or piece of gauze is introduced for drainage. The vagina is then loosely packed with iodoform gauze.

Combined Vaginal and Abdominal Hysterectomy.—A combined vaginal and abdominal hysterectomy is sometimes performed in order to enable the surgeon to deal with adhesions or complications in the upper part of the pelvis, or when the vagina is small and the uterus enlarged. It may be begun below and proceeded with until the uterine arteries are tied as in vaginal hysterectomy. The abdomen is then opened and the operation is finished from above, the uterus being taken out through the abdominal incision. It is preferable, however, to reverse this order of removal and perform the abdominal portion first, as there is less risk of infection. Complete abdominal hysterectomy is preferred by many operators.

The treatment of sarcoma and carcinoma of the body differs in no essential from that of the cervix. Hysterectomy is indicated in all cases as soon as the diagnosis is established and it is ascertained that the disease has not extended beyond the possibility of removal. Should the case be deemed inoperable, palliative measures are to be adopted as were recommended in this form of treatment for cancer of the cervix.

In case of cancer of the cervix complicating pregnancy, the following operations may be adopted, according to the special conditions of each case. "(*a*) Induced labor with hysterectomy after a few days; (*b*) Cæsarean section with colpohysterectomy later; (*c*) Supravaginal hysterectomy (Porro), followed at once by vaginal removal of the remainder of the uterus; (*d*) Total extirpation of the gravid uterus with dissection of the vagina by laparotomy" (Pozzi).

In the treatment of *deciduoma malignum* early and thorough removal of the affected part or parts is the only proper course to pursue A careful physical examination should be made, however, with the view of detecting metastatic deposits in the lungs and other organs, as their existence contraindicates operation. Metastases to the bladder, vagina, rectum, or uterine appendages are not absolute contraindications as these organs may be extirpated if necessary. The danger from delay is too evident in the foregoing description of this disease to require further emphasis, and in the light of past experience the gynecologist who postpones operation for the shortest time without some thoroughly sufficient excuse lays himself open to the grave and just criticism of wilfully lessening the patient's already too meagre chances of recovery.

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